PHD

The synthesis of benzoellipticine.

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THE SYNTHESIS

OF

BENZOELLIPTICINE

Submitted by Ian Matthews

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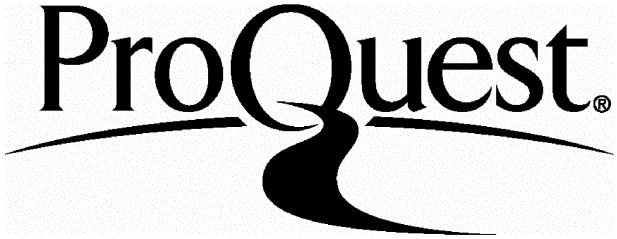
1978



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Finally, my gratitude goes to Annette for her endless patience.

SUMMARY

This thesis describes attempted preparations of 7,8-benzoellipticine and includes some detailed preparative chemistry of benzoindoles and benzocarbazoles. A successful preparation of 8,9-benzoellipticine is also described.

The work beings with a pharmacological discussion of ellipticine and its derivatives and gives a review of the published preparative methods, and concludes with a suggested synthesis of 7,8-benzoellipticine.

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INSTRUMENTAL METHODS

Perkin-Elmer infrared spectrophotometers - models 237 and 197 were used to obtain infrared spectra, employing the use of a Nujol mull.

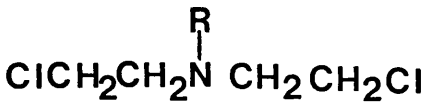
Ultraviolet spectra were obtained from a Perkin-Elmer ultraviolet spectrophotometer model 402, using methanol as the solvent.

An A.E.I. MS12 provided the mass spectrometric analysis and proton nuclear magnetic resonance spectra were obtained from a J.O.E.L. P.S. 100.

All melting points are uncorrected and the elemental analysis was carried out by Dr. F.B. Strauss, 10, Carlton Road, Oxford.

INTRODUCTION

The hope that cancer will ultimately prove amenable to certain forms of chemical treatment has long been entertained, but currently this expectation has only been partially fulfilled[1]. Most of the antineoplastic drugs available today are cytotoxic - simply destroying cells in general - they comprise certain alkylating agents, antibiotics and antimetabolites.
So far the alkylating agents are the only class of anti-tumour agents known to react with macromolecules, i.e. DNA and RNA, and produce covalent bonds[2]. Alkylating agents fall into several structurally distinct types, the nitrogen mustards (1) being one of these.

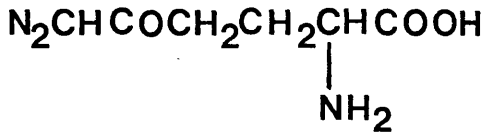


R=Alkyl, Acids etc.

bis-(2-chloroethyl)amino compounds

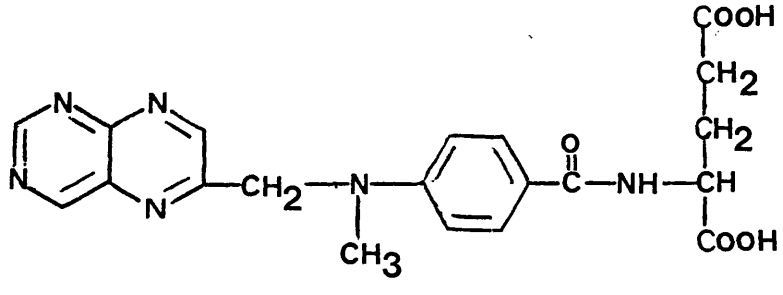
(1)

The antitumour antibiotics are a class of compounds which, in general, are produced by the Streptomyces[3] genus of soil bacteria. The antibiotic 6-diazo-5-oxo-L-norleucine (DON) (2) is one of these and is considered to be a glutamate antagonist and inhibits the purine skeleton synthesis.



(2)

The third class of antitumour agents are the antimetabolites, methotrexate (3) is one example. They are, by definition, substances which interfere with the formation or function of a natural metabolite. Methotrexate closely resembles folic acid in structure and this similarity allows methotrexate to compete with folic acid for the binding site on an enzyme, folate reductase, which normally converts the vitamin into a substance essential for the biosynthesis of amino acid bases, later incorporated into RNA and DNA.



(3)

The synthesis of substances with antineoplastic activity is a rapidly expanding field and the number of compounds effective against experimental neoplasms abounds. Despite this abundance, however, there are still very few drugs that are of any clinical

value, and the number of agents that are recognised in the treatment of human cancer is relatively small. Part of the reason for these disappointing conclusions lies in the fact that many of the experimental tumours used for initial recognition of antineoplastic agents are unsatisfactory models for further clinical development.

These are, in general, transplanted fast growing tumours. Drugs selected to combat these types of neoplasms are antigrowth rather than antitumour. Such types of animal tumours are generally preferred because spontaneous animal tumours do not show reproducible growth rates, although it is hoped that neoplasms may now be grown that are responsive to selective agents. For example certain transplanted lymphomas are asparaginase dependent and doses of the enzyme asparaginase[4] appear to cure the neoplasm.

It is thought that asparaginase causes an increase in ribonuclease activity in those tumours which subsequently regress[5]. This may be due to the removal, by asparaginase, of an inhibitor of ribonuclease. This inhibitor may only be present in certain lymphomas. So far no comparable disease has been found in man, although asparaginase itself, however, has a limited use in the production of short term remissions in some cases of acute lymphoblastic leukemia and in a small number of acute myeloblastic cases.
However, resistance to the enzyme develops rapidly.

Cancer is, of course, not one disease but an aggregation of many; this adds to the complexity of the problem but if antineoplastic drugs can be specifically designed for a given disease then its mode of action can be studied and progress towards an effective human drug may be accelerated.

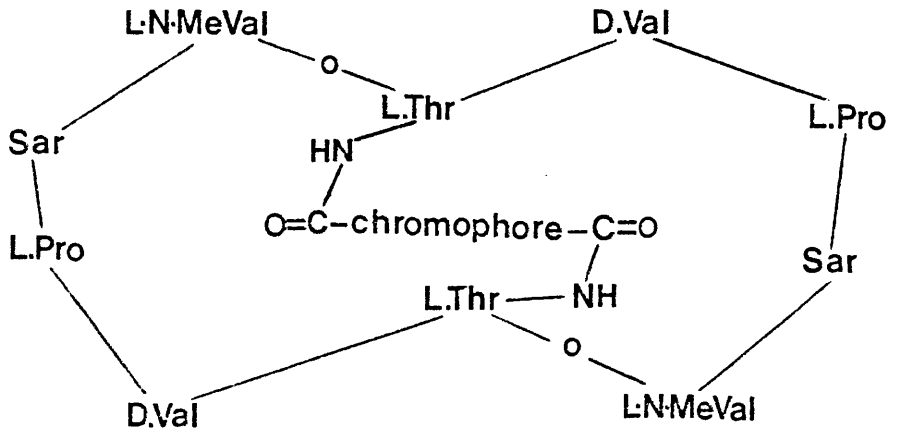
One group of compounds which seem to act in a similar manner are the intercalating agents. Intercalation is a well understood process and many of the strongest anti-cancer drugs known, such as Actinomycin D, Adriamycin and the acridines are intercalating agents. The ability of drugs to intercalate in DNA is conditioned by their stereochemical parameters, such as size and planarity as well as by their electronic configuration which controls the size of the intercalation energy with DNA[6] and of course the ability of the drug to cross the cell membranes. The drug must be in some way a mould of the cavity formed in DNA when two adjacent base pairs "unstake" as a result of the dynamic structure of DNA[7,8].

Generally, intercalating agents are of the correct spatial type to fit between the base pairs of the DNA helical structure and once in position they are secured by hydrogen bonding or perhaps by covalent bonding brought about through secondary chemical reactions in situ.

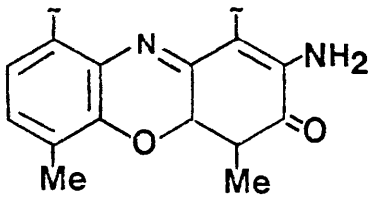
However, there is only one class of compounds - the actinomycins - for which the site and nature of the bonds have been worked out[9].

The chief metabolic effect of actinomycin is as an inhibitor of RNA synthesis which results from the binding of the inhibitor to DNA. The drug is bound to the deoxyguanylic moiety in the small groove of the double helix, as shown below;

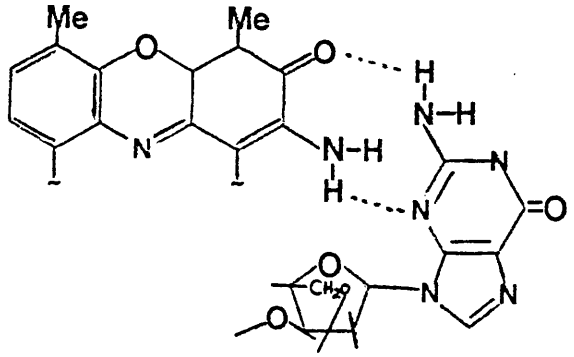
Actinomycin D



Chromophore



Hydrogen Bonding to Nucleoside

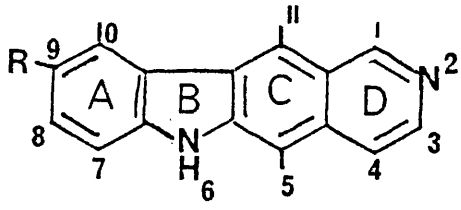


In addition to the hydrogen bonds shown, the -NH- groups of the polypeptide chains of actinomycin can form hydrogen bonds with the phosphate oxygen atoms of the DNA strand.

The circular structure of intact mitochondrial DNA possesses a high binding affinity towards compounds that are known to intercalate since nearly selective binding of acridine dyes and ethidium bromide to mitochondrial DNA occurs[10].

If DNA is the best site to attack for antitumour activity, then it should be possible to design a drug with the highest possible affinity for DNA. A study of the pharmacological activity of antineoplastic agents should allow the design of an active anticancer drug.

Some time ago two alkaloids, ellipticine (4) and its 9-methoxy derivative (5), were extracted from small trees of the Ochrosia[11] genus indigenous to the Pacific Islands and Australia. These compounds stimulated a great deal of interest, due to their antineoplastic activity, notably against human myeloblastic leukemia[12].



R=H (4)
R=OMe (5)

It was found that ellipticine and its 9- substituted derivative fitted the theoretical design for an intercalating drug very well. The size and arc-shaped form of these alkaloids was remarkably similar to some of the most strongly active intercalating substances. A great deal of study into the properties of these alkaloids with relation to the DNA conformation, affinity and unwinding angle has been carried out, in order to design a more effective antitumour agent. This study led to the design and synthesis of 9-hydroxyellipticine, which has been found to have a very high activity against human leukemia; and is relatively non-toxic.

So far no other derivative of ellipticine has shown greater antineoplastic activity against the experimental L1210 tumour than 9-hydroxyellipticine. Instrumental to the discovery of 9-hydroxyellipticine was a Hansch analysis[13] conducted some time ago and implemented by synthetic studies in France and at Bath.

This approach depends upon the recognition that the physicochemical properties associated with a substituted group may be loosely classified as electronic, steric or solvent partitioning. A judicious choice of which substituents to insert into the parent structure in order to achieve greater pharmacological activity may then be made on a compromise basis taking these three factors into account.

By far the greater majority of published studies on this subject have been based on Hansch's π [14,15] equation, often augmented by the Hammett equation and occasionally by one or more of the other properties. The Hansch π value of a substituent is defined as log (P/P_0) where P is the partition coefficient between octanol and water for the substituted compound, and P_0 the coefficient for the unsubstituted compound. In general, most useful drugs have a value of log P in the range of 0-6. Therefore, assuming a log P value of 4 for ellipticine, then substituents with π values of -3.5 - 2.0 should be considered as likely candidates.

This value is not only essentially independent of compound series, but is also well approximated for an unknown substituent by summing the values of the substituent fragments [16]. This additive property of values is useful when a compound containing a new substituent is being considered.

Thus for 5, 11-desmethylellipticine log P is calculated as follows:

$$\pi C_6H_5NH + \text{Log P (isoquinoline)} = 1.37 + 2.08 = 3.45$$

where $\pi C_6H_5NH = \text{Log P } (C_6H_5)_2NH - \text{Log P } C_6H_6$

$$= 3.5 - 2.13 - 1.37$$

Log P for 11-desmethylellipticine has been measured and its value

is 4.06. Subtracting 0.5 (πCH_3) from this we obtain a calculated value for the parent compound of 3.56 which correlates well with the above calculated value of 3.45.

Recently Le Pecq et al[17] have investigated the relationship between the physicochemical properties of ellipticine and their affinity for DNA at physiological pH. This study also enabled them to examine the relationship between DNA reactivity of ellipticine and its derivatives and their anticancerous properties.

This group were able to compute[18] the DNA binding constant of the protonated ellipticine derivative, K_E^+ from variations of the DNA binding constant, K_{ap}, as a function of pH, as follows:

$$\text{Log } K_{ap} = \text{Log } K_E^+ - \text{Log}(1 + K_H^{-1}/[H^+]) + \text{Log}(1 + K_H^{-1}/\alpha[H^+])$$

where K_H^{-1} is the dissociation constant of the equilibrium between the protonated and non-protonated drug and α is the ratio of the DNA binding constant of the protonated and neutral form of the drug.

The unwinding angle of the DNA helix caused by intercalation of each ellipticine derivative was also measured.

A summary of the results of these calculations along with their activities is tabulated in table 1.

The influence of pKa on the activity of ellipticine derivatives is seen when comparing ellipticine and 11 -desmethylellipticine. The loss of the single methyl group from the 11 position causes a pKa drop of 3 units and thus a 10-fold decrease of the DNA binding constant. Since the binding constants K_E^+ of these derivatives are similar the authors suggest that the variation in pKa is the only intervening factor to account for the difference in activity.

TABLE 1

ELLIPTICINE DERIVATIVE	pKa	Kap(pH7.4)	Ø	$LogK_E$+	ACTIVITY
6-isopentyl	4.7	10^4	6.3	8.8	0
6-isopentyl-9-methoxy	4.5	10^4	6.7	-	-
5,11-desmethyl	6.35	$1.0x10^4$	5.08	-	0
11,-desmethyl	6.3	$2.4x10^4$	5.52	-	0
9-methoxy	6.8	$1.0x10^5$	5.7	6.8	90
ellipticine	9.1	$1.5x10^5$	5.2	9	94
9-bromo	6.1	$4.0x10^5$	6.92	0	0
6-methyl	6.1	$4.0x10^5$	6.92	10.2	92
9-amino	9.8	$1.2x10^6$	6.08	4	2
6-methyl-9-methoxy	6.45	$2.0x10^6$	7.3	5	50
9-hydroxy	9.8	$2.0x10^6$	6.15	12	99.96

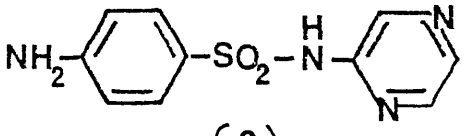
[Ø = Unwinding angle; Activity = % of L1210 cells killed by 1/3rd of LD_{50}. 9-bromoellipticine does not intercalate.]

The Hansch approach is to take a biologically active compound and study the effects of substituents on its activity with a view to finding the most effective substituent. Theoretical work carried out by Hansch suggested that the pKa of ellipticine might be increased by further conjugation with a phenyl group on the 9 position. Consideration of the Watson and Crick molecular model, however, indicated that 9-phenylellipticine would be unsuitable for intercalation due to steric hinderance; it would also be very lipophilic. 9-phenylellipticine was duly synthesised[19] and found to be inactive, thus providing circumstantial evidence in favour of the intercalation role suspected for the ellipticines.

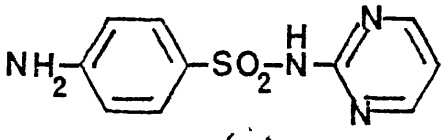
To overcome this non-planarity problem it was decided to synthesise benzoellipticine derivatives. In this way the electronic effects deemed desirable by Hansch would be achieved but the derivatives themselves would still be flat.

This work forms the basis of this thesis, but in parallel, other work in the laboratory centres upon 9-aminoellipticine, since theoretical calculations predict that this derivative would have considerable activity. On testing, however, it was found to be inactive against the L1210 mouse tumour cells, but it is mutagenic and it is excreted by test animals as the acetamido derivative. To overcome the mutagenic and metabolic properties of this compound a number of ideas have been proposed. Thus substituting a methyl group in the A ring, ortho to the amino group might have the effect of preventing its mutagenicity i.e. 2-naphthylamine is mutagenic but 1-methyl-2-naphthylamine is not.

Additionally, work carried out by Conners *et al*[20] on sulphonamides has shown that sulphapyrazine (6) and sulphadiazine (7) concentrate in tumour cells.



(6)



(7)

This is thought to be due to two reasons; firstly that tumour cells are somewhat more acidic than normal cells and secondly that an equilibrium exists between the ionic soluble form of the drug and the insoluble neutral form. Therefore as the drug is basic it tends to concentrate in tumour cells.

In view of this it is the aim of workers in this laboratory to prepare 9-sulphonamidoellipticines in order to test some of these theories.

Ellipticine exists in two equilibrate forms; a neutral and a cationic form. The cationic form has thirty times more DNA binding power than has the neutral form.

Further investigations undertaken by French workers[21] have shown that ellipticine in humans is hydroxylated in two positions; the 7 and the 9 position. Presumably this may be how the drug is activated and it is suggested that 9-hydroxyellipticine is then oxidised as the cationic form to a quinone type structure which then intercalates with the DNA base pairs. Re-aromatisation occurs and the DNA is twisted out of shape, thus not allowing any further protein synthesis. The 7-hydroxy and 9-hydroxyellipticine have been examined separately, and it transpires that 7-hydroxyellipticine is inactive against the experimental tumours it was tested on. As mentioned previously the 9-hydroxyellipticine is highly active.

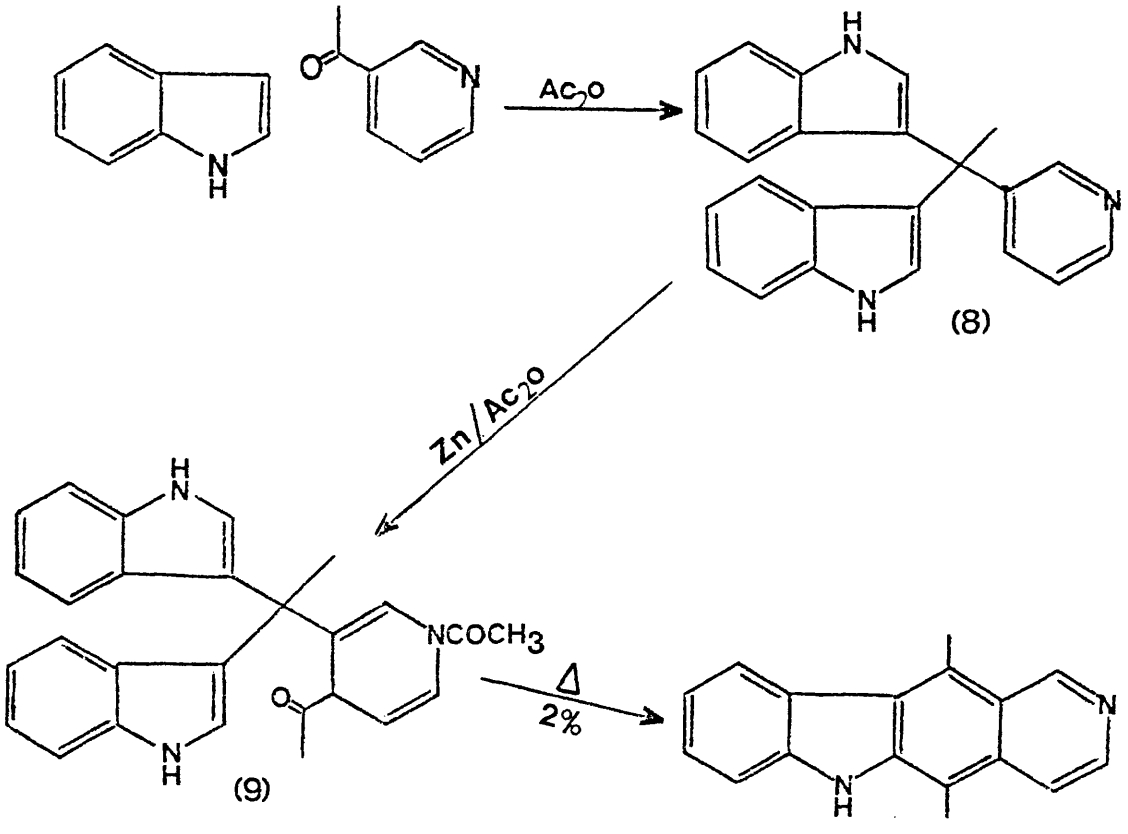
The position of the base pairs relative to the electronegative and electropositive centres in ellipticine appears to be critical. Work at the present is aimed at the synthesis of the 8- and 10-hydroxy-ellipticines.

SYNTHETIC ROUTES TO ELLIPTICINE

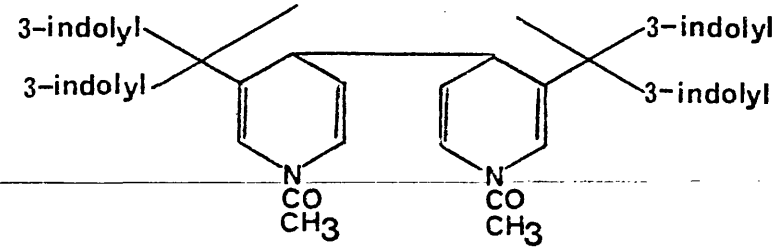
Since the discovery of ellipticine[22] and its 9-methoxy derivative in plants belonging to the Apocyanaceae family, there has been great interest in the synthesis of this alkaloid and its derivatives, mainly because of their potential as anticancer agents[23].

The earliest reported synthesis, published very rapidly after the discovery of ellipticine, was carried out by Woodward et al[24], this seemed to confirm its structure. In this work a diindolylethyl-pyridine (8) was formed by the reaction of one mol. of 3 acetylpyridine with two mol. of indole in the presence of acetic anhydride. Reductive acetylation involving zinc and acetic anhydride afforded the 1 ,4-diacetyldihydropyridine (9). Pyrolysis of this product gave ellipticine in very small yield.

ROUTE 1



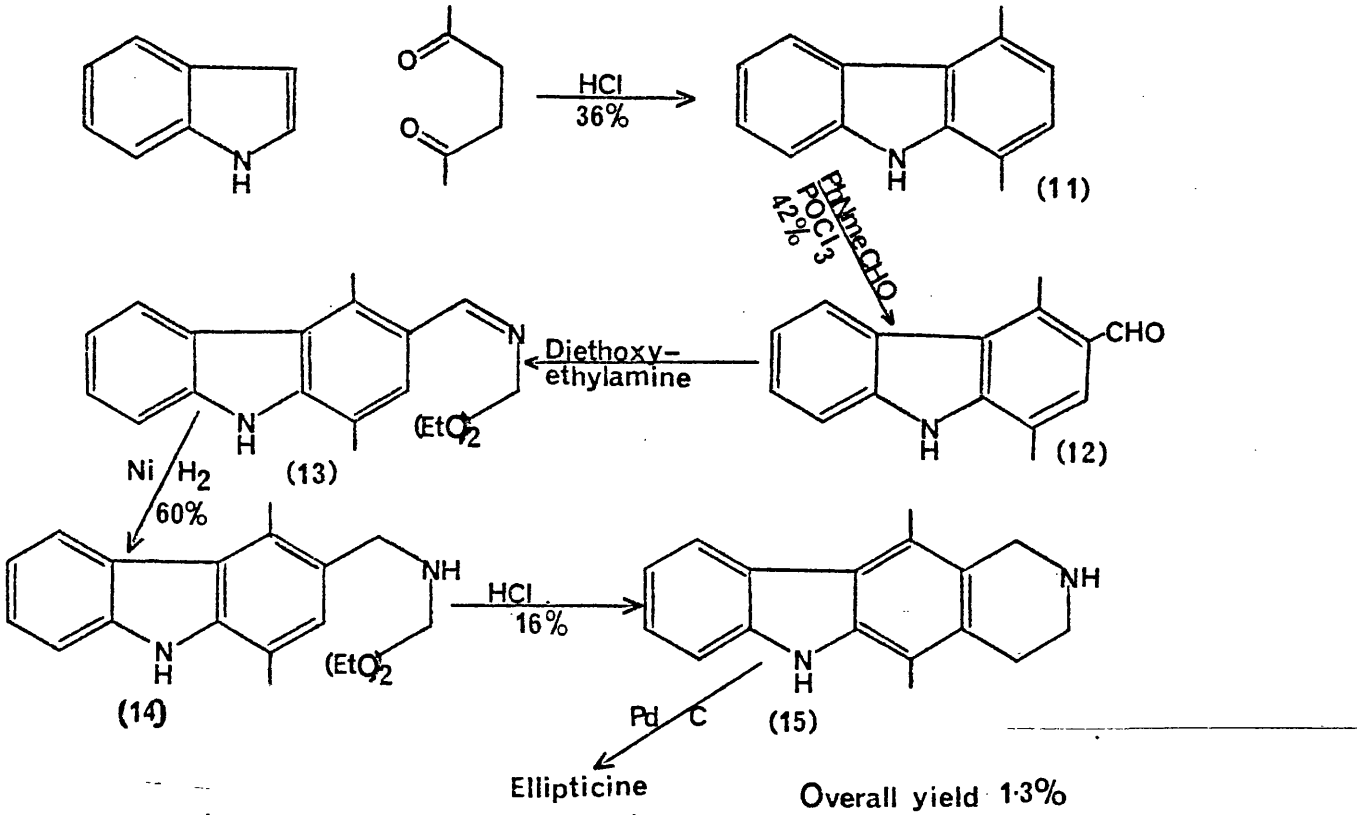
One of the main reasons for the low yields quoted for this route may be that the formation of a highly hindered dimer is required during the reductive acetylation step. Such a compound (10) is unlikely to form easily and moreover according to Atlani[25] et al it is then said to undergo disproportionation into (9) and starting material. At best then, product yield can only be 50% and substrate (9) is hardly an ideal intermediate for ellipticine.



(10)

A second synthetic route to ellipticine (Route 2) shortly followed this pioneering study and has proved to be one of the most profitable and versatile routes designed so far. This pathway, reported by Cranwell and Saxton[26,27], requires 1,4-dimethylcarbazole (11) formed by the acid condensation of indole and hexane-2,5-dione. The carbazole is then converted into the 3-formyl derivative (12) from which the Schiff's base is prepared (13). At first, attempts to prepare ellipticine directly from the Schiff's base failed but on reduction to the amine (14), dihydroellipticine (15) is formed from an acid cyclisation. The oxidative step is achieved by heating with palladium on charcoal.

ROUTE 2

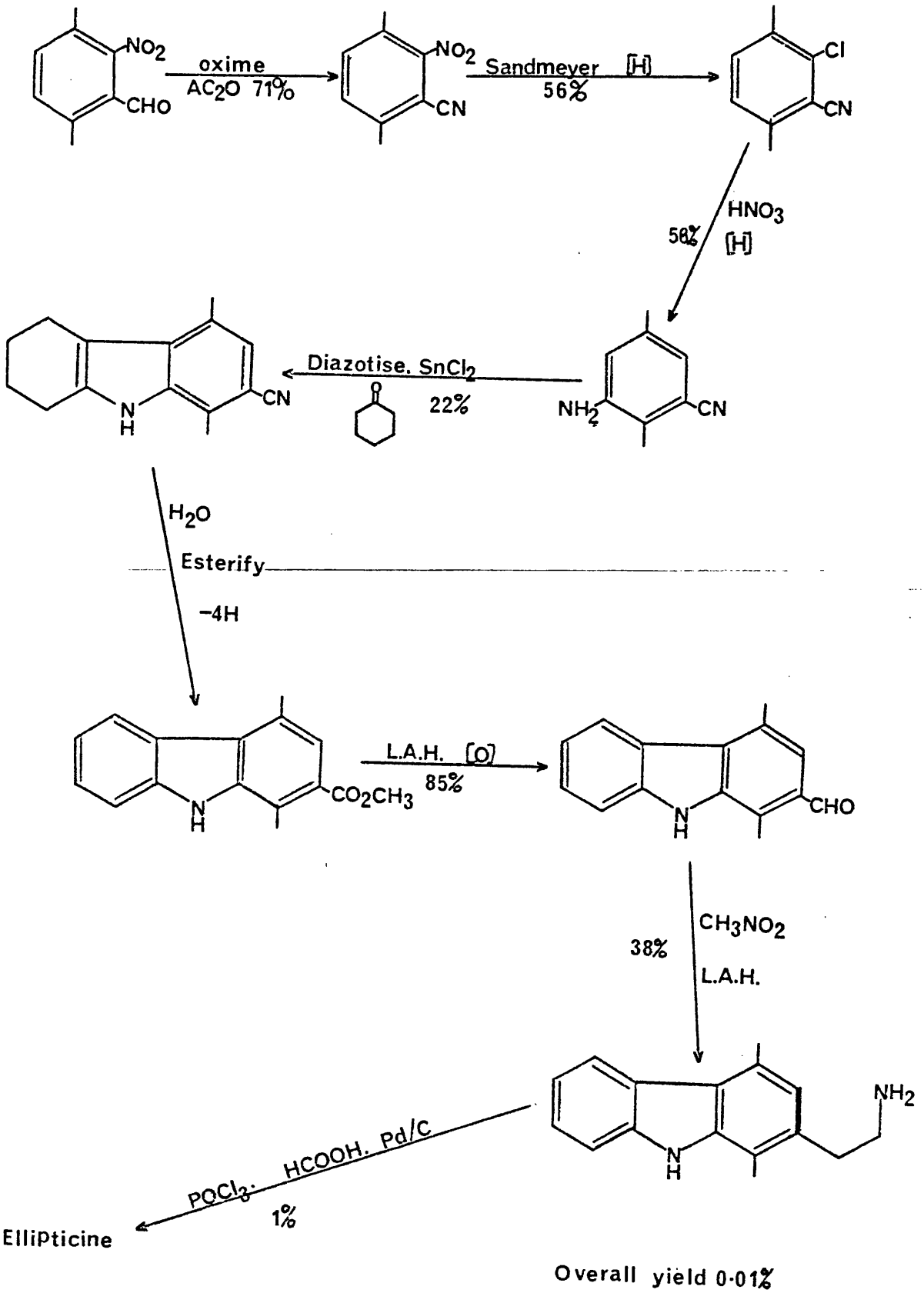


Following on from these two relatively short syntheses two others were described, they serve as lessons in synthetic manipulation but both are very lengthy and consequently the yields are very low.

The first of these by Govindachari et al[28] (Route 3) approaches the synthesis of the alkaloid by first constructing ring C and then simultaneously building on rings A and B. Further manipulation of ring C allowed the ultimate addition of ring D.

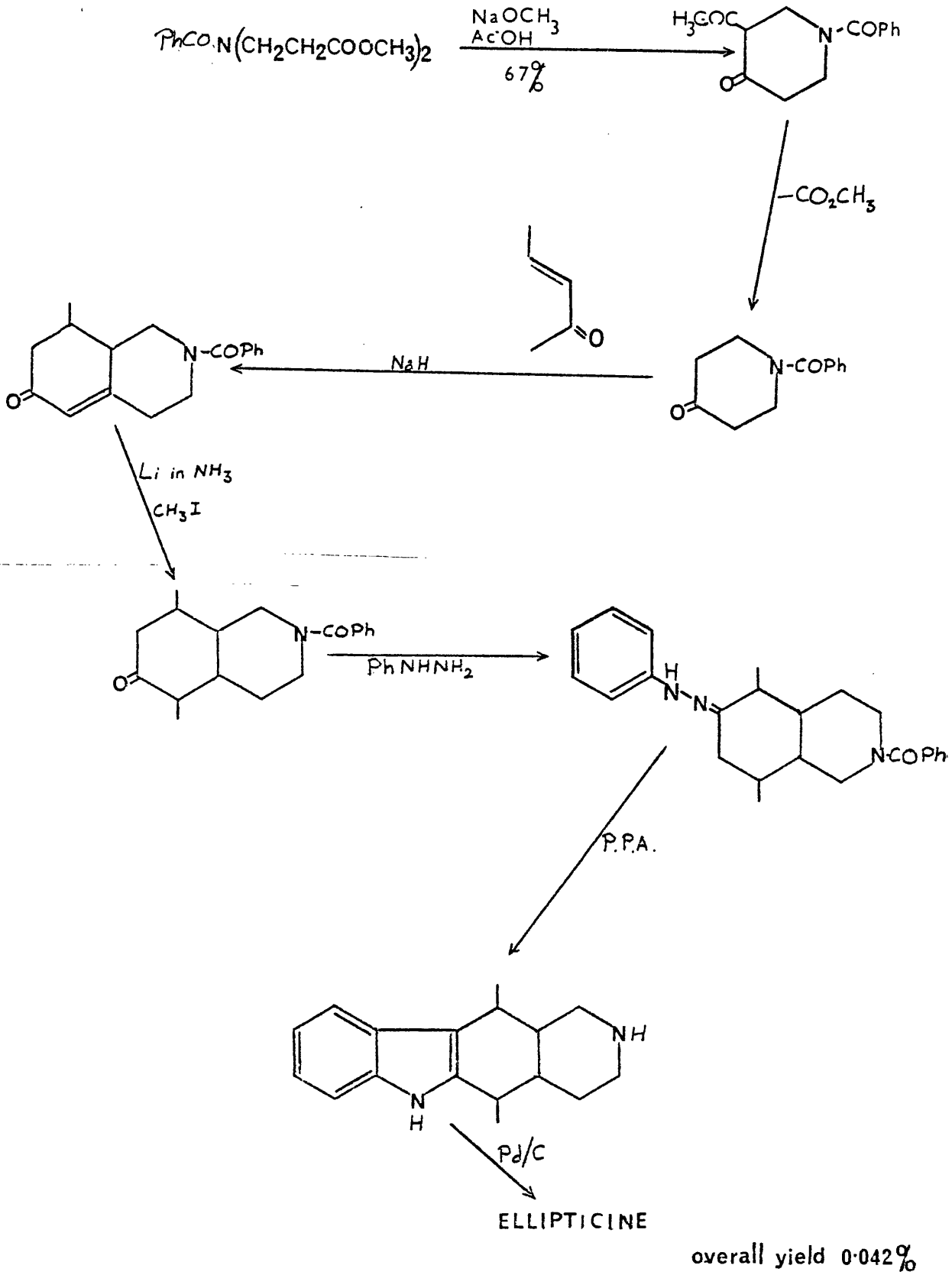
The second approach due to Stillwell[29] (Route 4) concerns itself with the formation of the C/D ring system using an appropriately substituted isoquinoline moiety, and then builds the ellipticine skeleton using a Fischer indolisation reaction.

ROUTE 3



Overall yield 0·01%

ROUTE 4



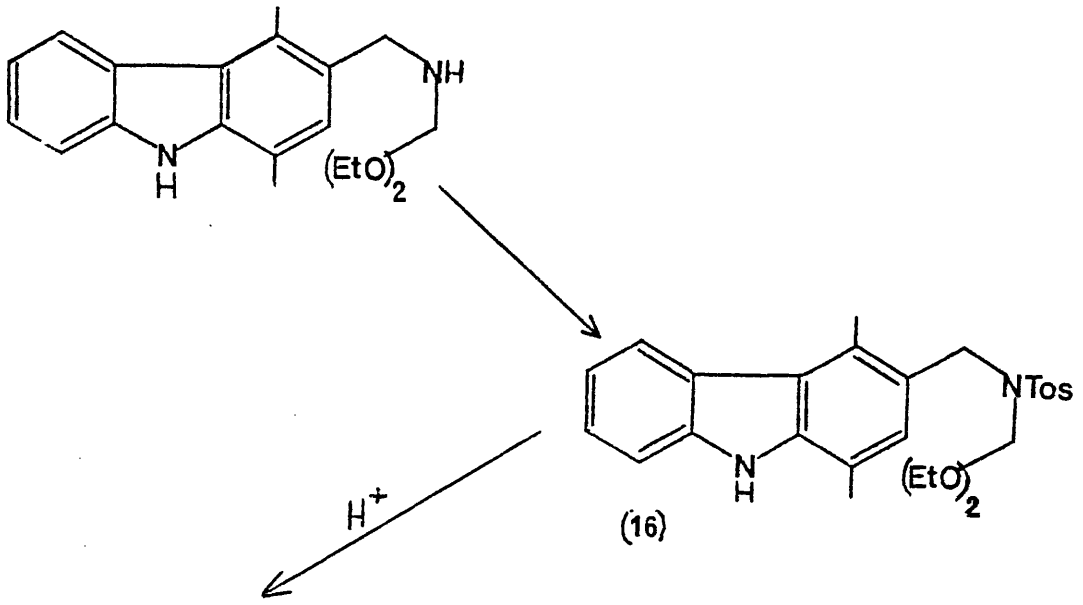
overall yield 0·042%

By this method derivatives such as 9-fluoro, 9-methyl, 9-methoxy and 7-fluoroellipticine have been prepared, but their biological properties are still unknown.

Work carried out by Dalton et al[30] showed that the yield of ellipticine produced from the Cranwell and Saxton method could be substantially improved by employing 100% phosphoric acid upon the azomethine (13), thus producing ellipticine in one step instead of the original three. Dalton also found that this ring closure was affected by the presence of electron donating and withdrawing groups. The presence of electron withdrawing functions in ring A decreased the amount of ring closed product, whereas electron donating groups increased the yield. Unfortunately, the presence of electron donating functions in ring A also causes the formation of a mixture of formyl products; the required formylated product (11) along with carbazoles formylated in Ring A. The amount of the required formyl carbazole depended on the position of the electron donating substituent in ring A.

Guthrie[31] et al have recently developed a second modification to Cranwell and Saxton's route. This author prepared the amine (13) in the usual manner and then converted this to the N-p-toluenesulphonyl derivative (16). This compound, when treated with hydrochloric acid in dioxan, smoothly cyclised to ellipticine with the elimination of p-toluenesulphinic acid in 49% yield.

The presence of electron withdrawing groups in the A ring again had the unfortunate effect of drastically reducing the yields of ellipticine derivatives.



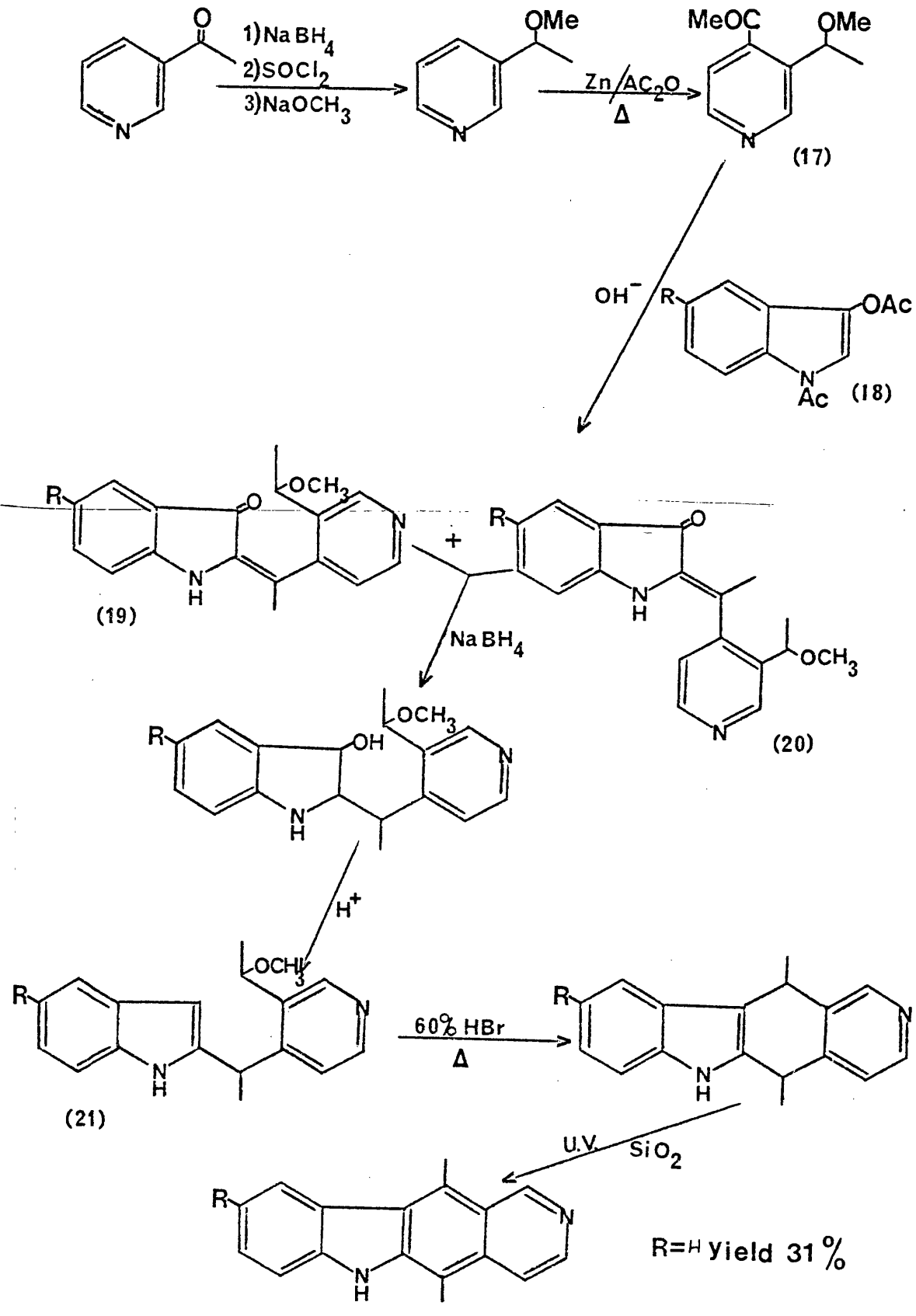
Ellipticine

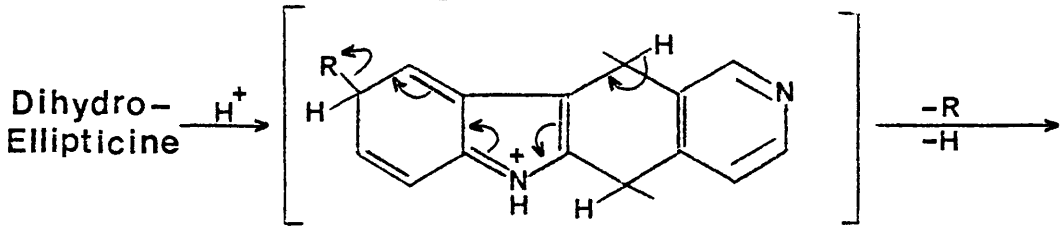
The most efficient and rewarding route yet designed came from work carried out by Kilminster and Sainsbury[32] in this laboratory. (Route 5).

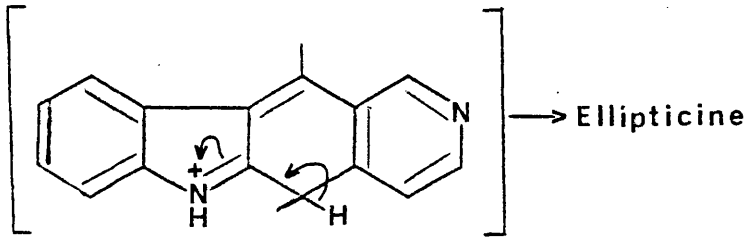
Here 4-acetyl-3-(1-methoxyethyl)pyridine (17) was condensed with a 1,3-diacetylindoxyl (18, R=H, NHAc and Br) to give a mixture of the (E) (19) and (Z) (20) isomers respectively. On treating the isomers with sodium borohydride and then dehydration with hydrogen chloride, the indole (21, R=H, NHAc and Br) was obtained. This, when heated under reflux with aqueous hydrobromic acid, afforded ellipticines in good yield.

One of the few minor drawbacks to this route shows itself in the reduced yields of 9-amino and 9-bromoellipticine. There, the hydrobromic acid ring closure reaction causes a certain amount of oxidative elimination of the substituent.

ROUTE 5


1) NaBH4
2) SOCl2
3) NaOCH3
OMe
MeOC
OMe
Zn/Ac2O
Δ
(17)
OH⁻
R
OAc
N
Ac
(18)
OCH3
R
O
N
H
(19)
+
NaBH4
OCH3
(20)
OH
H+
OCH3
60% HBr
Δ
(21)
U.V.
SiO2
R=H yield 31 %

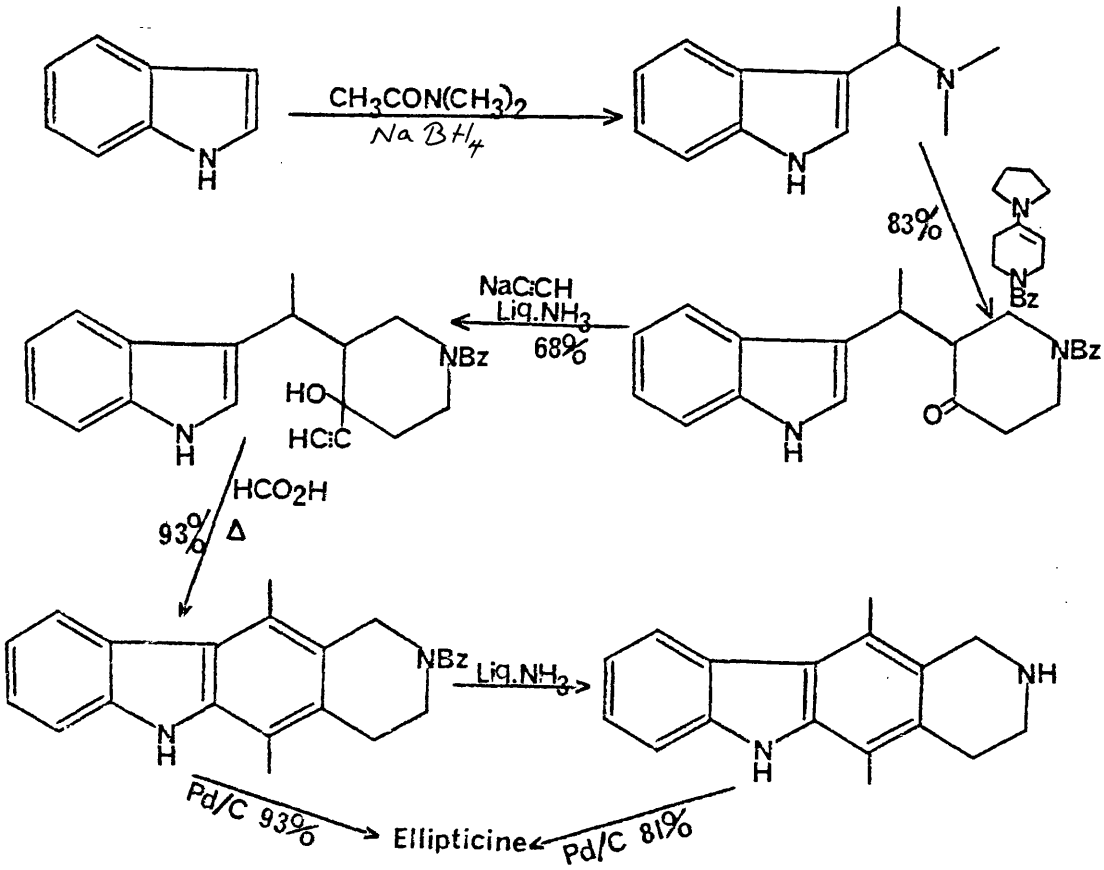




If, however, the substituent is not a good leaving group then the ellipticine is produced in excellent yields.

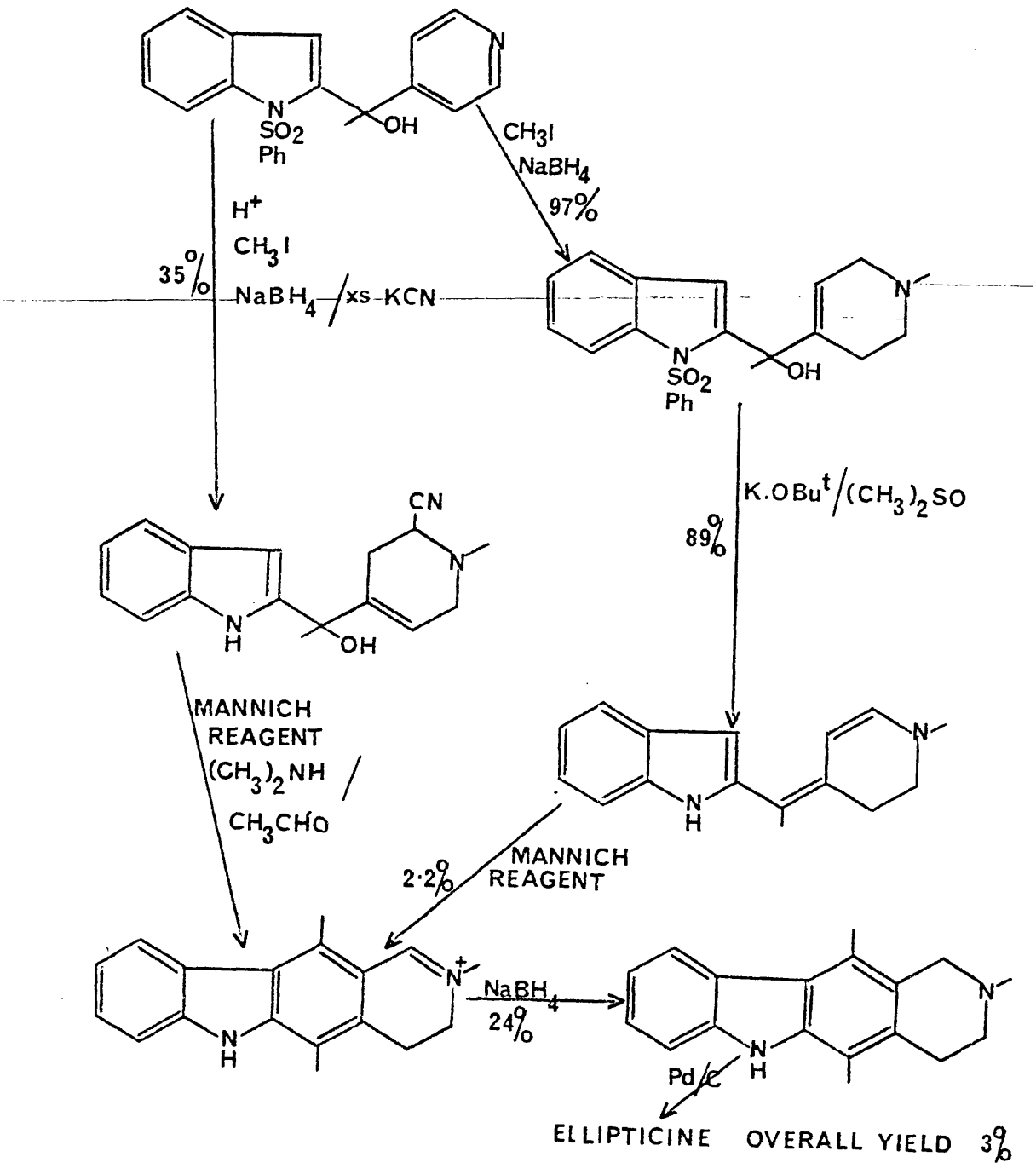
Another synthesis, pioneered by Le Goffic[33] et al produces ellipticine in an overall yield of 24%. This method was initiated by a Vielsmier-type condensation between indole and NN-dimethylacetamide (Route 6).

ROUTE 6



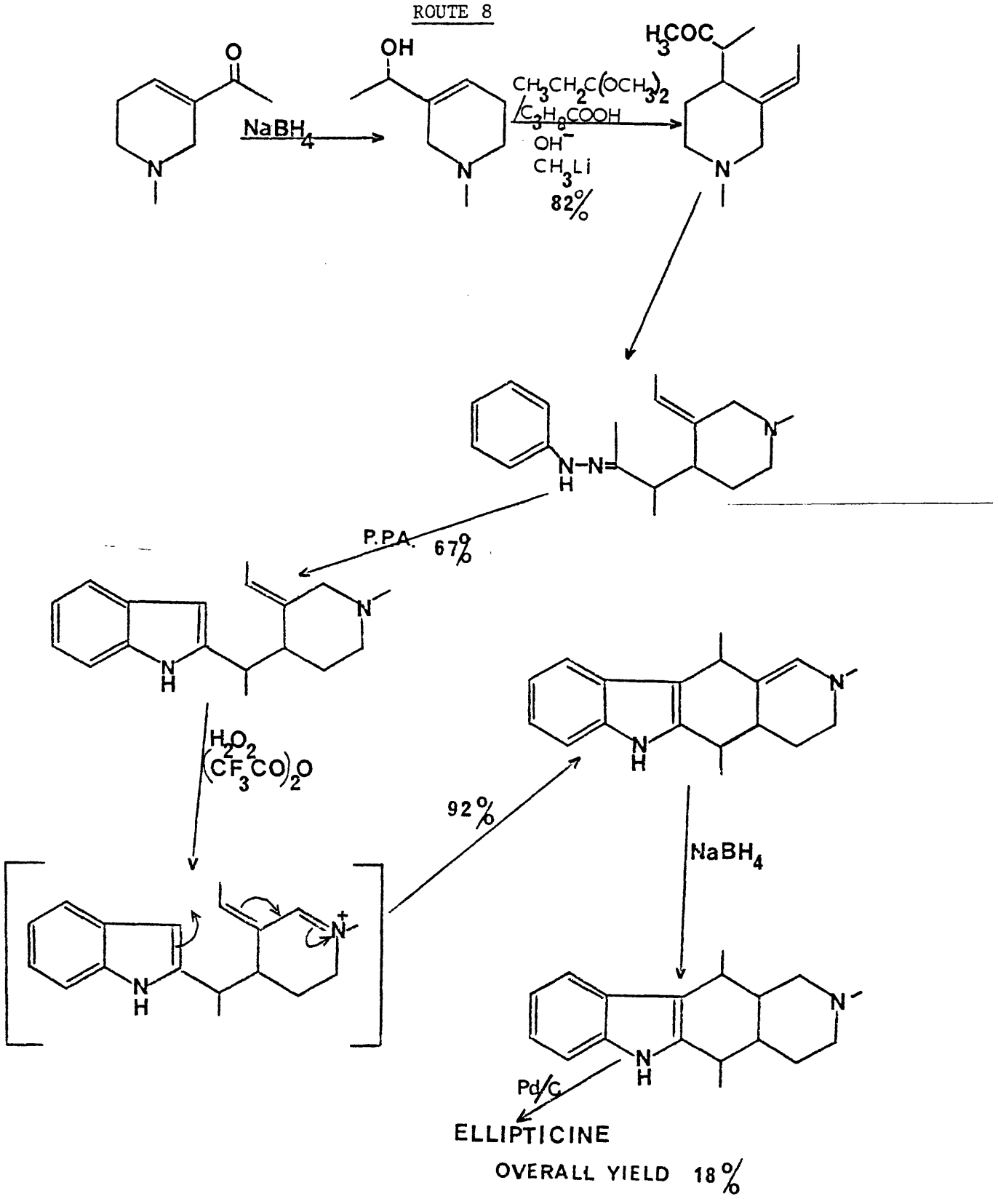
Yet another synthesis of ellipticine, based on a proposed biosynthetic pathway[34] is described by Potier[35] et al (Route 7) and this involves a Mannich reaction. The initial indole (22) is produced by reacting 2-lithio-1-sulphobenzoylindole with 4-acetyl pyridine.

ROUTE 7

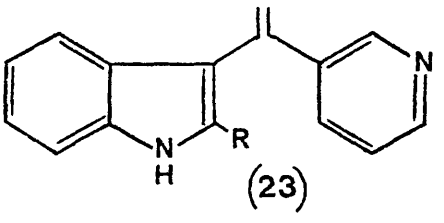


Still more work of French origin involves an elaborate but more efficient synthesis, which is summarised below in Route 8:

ROUTE 8



Work carried out by Bergmann and Carlsson[36] showed that indoles substituted in the 2-position, when condensed with 3-acetylpyridine in acetic acid produced compounds of the type (23) and not the undesired '1:2 condensation product'.



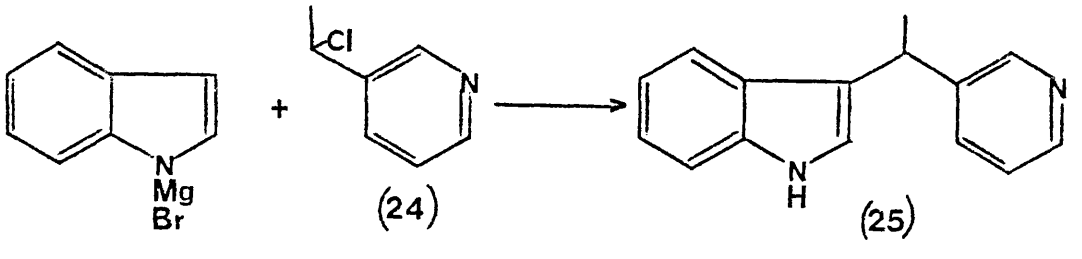
(23)

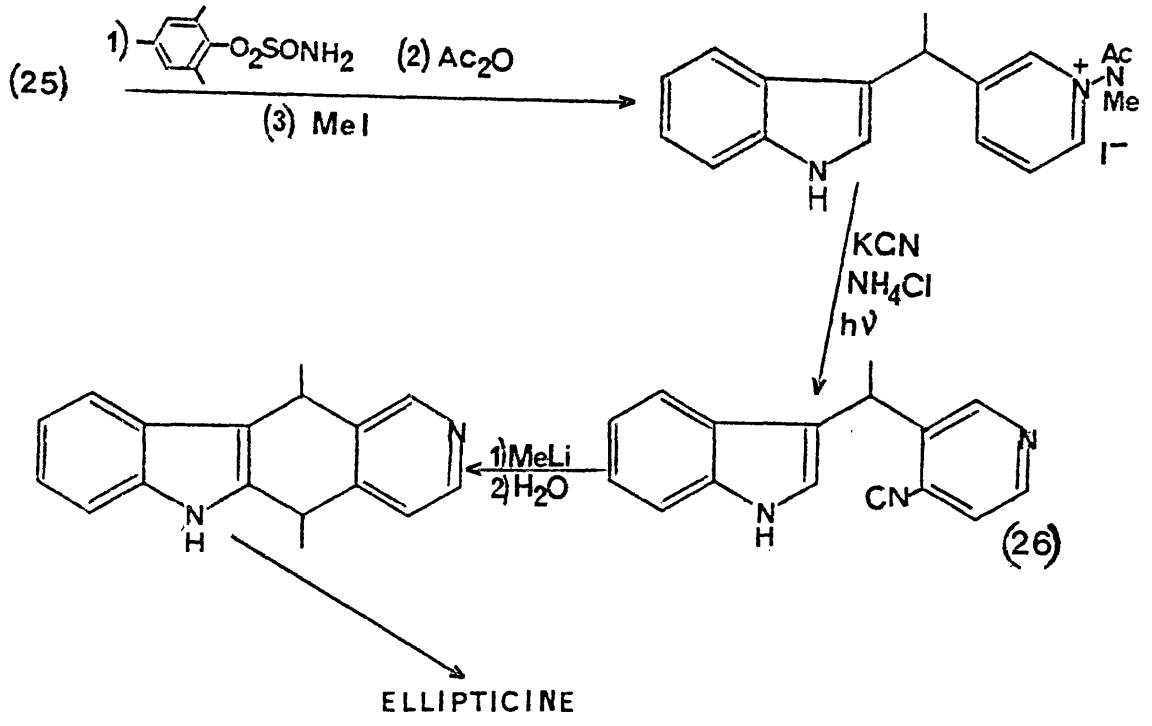
R=ALKYL

In such cases, however, steric hinderance of the 2-substituent readily accounts for the formation of a '1:1 product'. However, condensation of 3-acetylpyridine with unsubstituted indole, using the same solvent but using a variety of reaction conditions produces (8). The formation of this '2:1 product' is likely to be due to high reactivity toward electrophilic substitution; the 3-position being the most reactive site for substitution of indole.

Studies carried out in this laboratory[37] showed that indole magnesium bromide could be reacted with the chloropyridine (24) to give the '1:1 indole pyridine product' (25) instead of Woodwards' '2:1 product'. Also, during this work a highly efficient route to 4-acetylpyridine was devised. This enabled ellipticine to be prepared in modest yields using particularly mild conditions.

This route is summarised below:





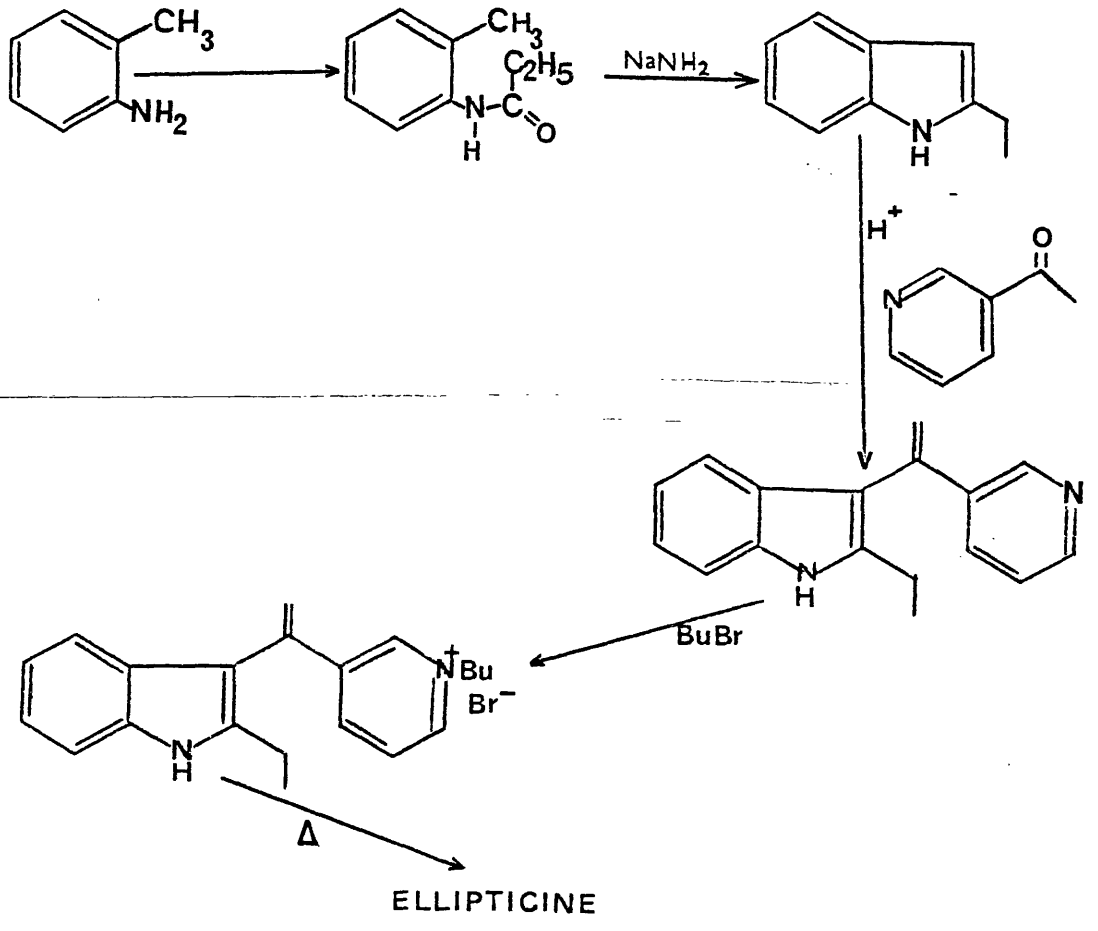
The cyanide (26) is treated with methyl lithium to produce the azomethine which is easily hydrolysed by refluxing with 20% acetic acid to produce ellipticine in overall yield of approximately 20%.

One of the more recent routes to ellipticine is due to Bergmann and Carlsson[38]. Here, the propensity of simple indoles to react with 2 mol. of ketones is eliminated by using 2-alkylindoles which afford the '1:1 products' in good yields.

2-ethylindole is easily prepared using the Madelung method and this is condensed, in excellent yields, with 3-acetylpyridine. The resulting product (27) is then quaternised by refluxing with butylbromide and this salt pyrolysed directly to ellipticine.

Bergmann's method claims greater than 70% overall yield from the indole, however, the final pyrolytic step precludes the use of labile substituents. Work is being carried out in this laboratory to increase the alkyl chain length by this method (Route 9).

ROUTE 9

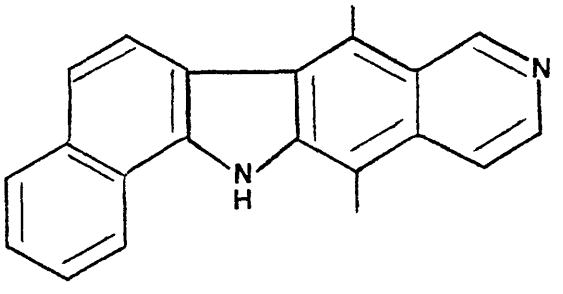


With the advent of more efficient, milder methods of ellipticine synthesis, the number of derivatives able to be prepared has greatly increased.

In the past the derivatives prepared showed ease of access rather than an attempt to study structure - activity relationships, the more recent methods allow such a study to be undertaken without too much detailed preparative chemistry.

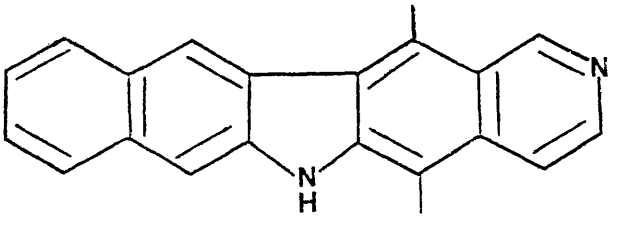
D I S C U S S I O N

The main aim of the work carried out in the course of this thesis was to attempt the preparation of the benzo derivatives of ellipticine, A, B and C, for biological testing. This would determine the extent of increased conjugation on the antineoplastic activity of ellipticine.



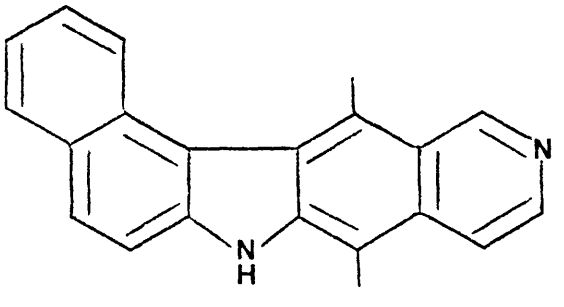
A

7,8-BENZOELLIPTICINE



B

8,9-BENZOELLIPTICINE



C

9,10-BENZOELLIPTICINE

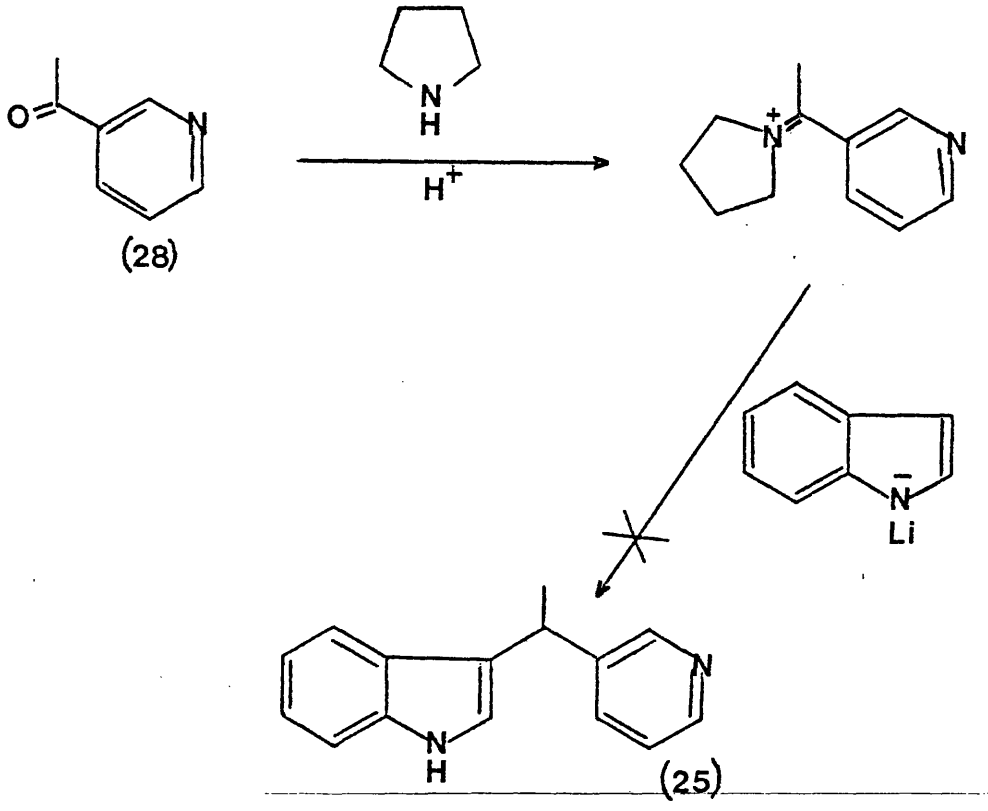
Synthesis of these compounds was attempted using modifications to some of the established routes already mentioned earlier but new methods of producing the indolyl pyridine (25) were also tried.

(i) New Synthesis of 3-[1-(3-pyridyl)ethyl] indole (25)

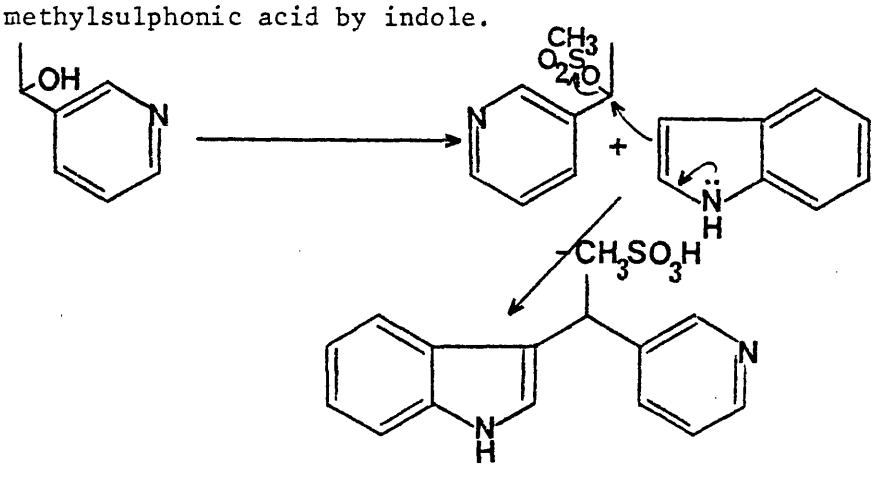
The original success of the condensation[37] between the indole Grignard and the chloropyridine (24) has sparked off new attempts at preparing the title compound in greater yield. This seems to be the only weak point in the synthesis since the subsequent steps work in excellent yields.

Initially, it was speculated that the lithio derivative of indole should react directly with 3-acetylpyridine to produce the desired compound (25). However, when n-butyllithium was used no reaction took place. When a variety of solvents and reaction conditions were employed only starting material was returned. It was thought that the reaction might proceed more readily if the carbonyl bond was more strongly polarised, and this was attempted by heating 3-acetylpyridine, pyrrolidene and a trace of p-toluenesulphonic acid in benzene, using a Dean and Stark apparatus. The resulting solution was slowly added to a suspension of lithio-indole in ether. This mixture was stirred for half an hour. The solid which formed was worked up for bases but produced only a mixture of pyrrolidene and 3-acetylpyridine. Indole was reclaimed from the ethereal layer.

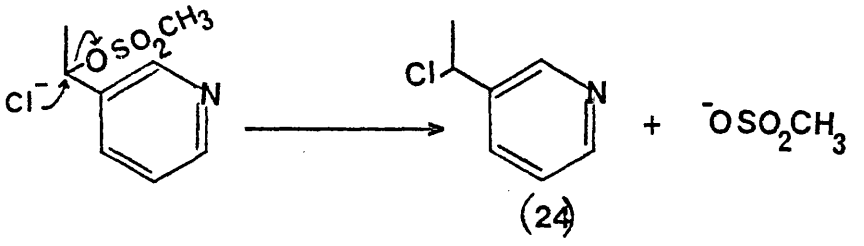
The attempted route is summarised below:-



A final attempt was made to prepare the title compound by refluxing a mixture of indole and 3-ethyl(1-hydroxy)-pyridine (28) in benzene, using a Dean and Stark apparatus, whilst methanesulphonyl chloride was added over a period of five hours. The resulting orange oil was dissolved in water and washed with ether to remove any unreacted indole. On basification and extraction a modest amount (30%) of the indole (25) was produced. The mechanism of the reaction, outlined below, is thought to be one of nucleophilic displacement of methylsulphonic acid by indole.

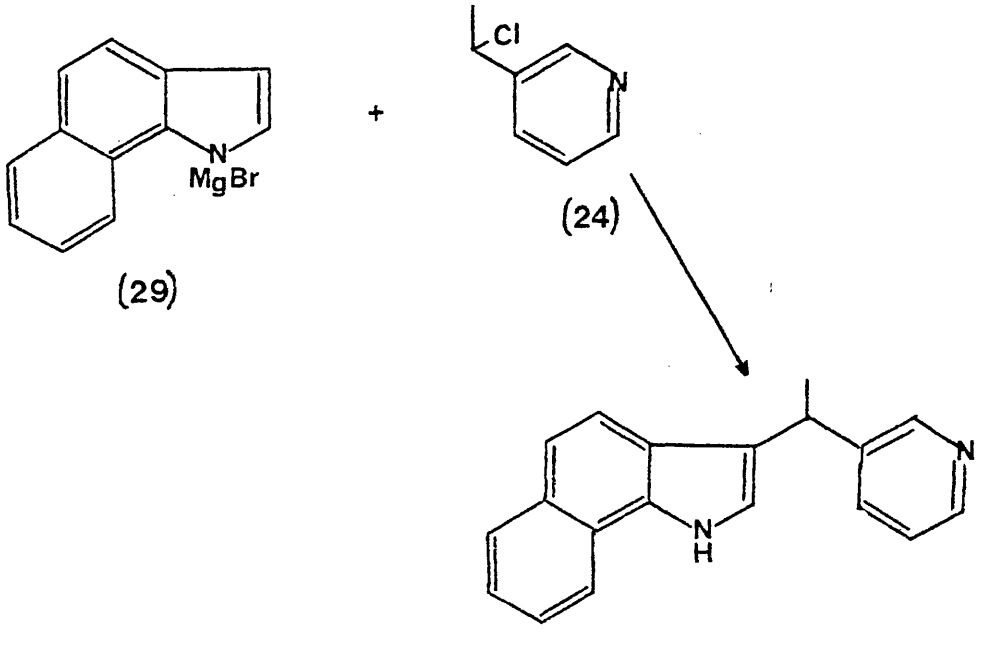


It is interesting that a major contaminant is the chloroethyl pyridine (24) formed, presumably, by attack of chloride ion at the α-position with elimination of the methanesulphonate anion.



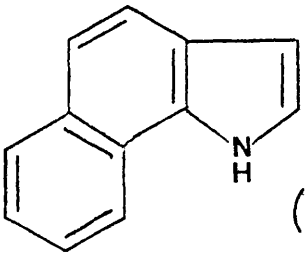
(24)

Unfortunately the indoles required for the synthesis of the benzoellipticines are not readily available and the poor yield obtained in these pilot experiments seem to indicate that a route based on this approach might be uneconomical, and so the method selected was that shown on page 24 and reproduced for isomer (29) below:



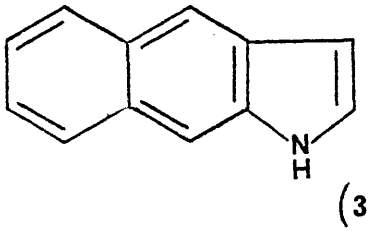
(29) (24)

The pyridine component could be prepared by a known synthetic route[37]. This would then only leave the preparation of the three benzoindole derivatives (29, 30 and 31) to be undertaken.



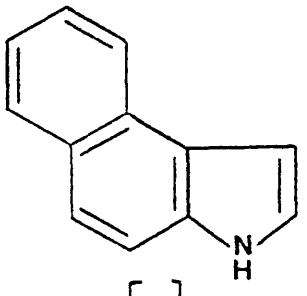
(29)

1H-BENZO [g] INDOLE



(30)

1H-BENZO [f] INDOLE



(31)

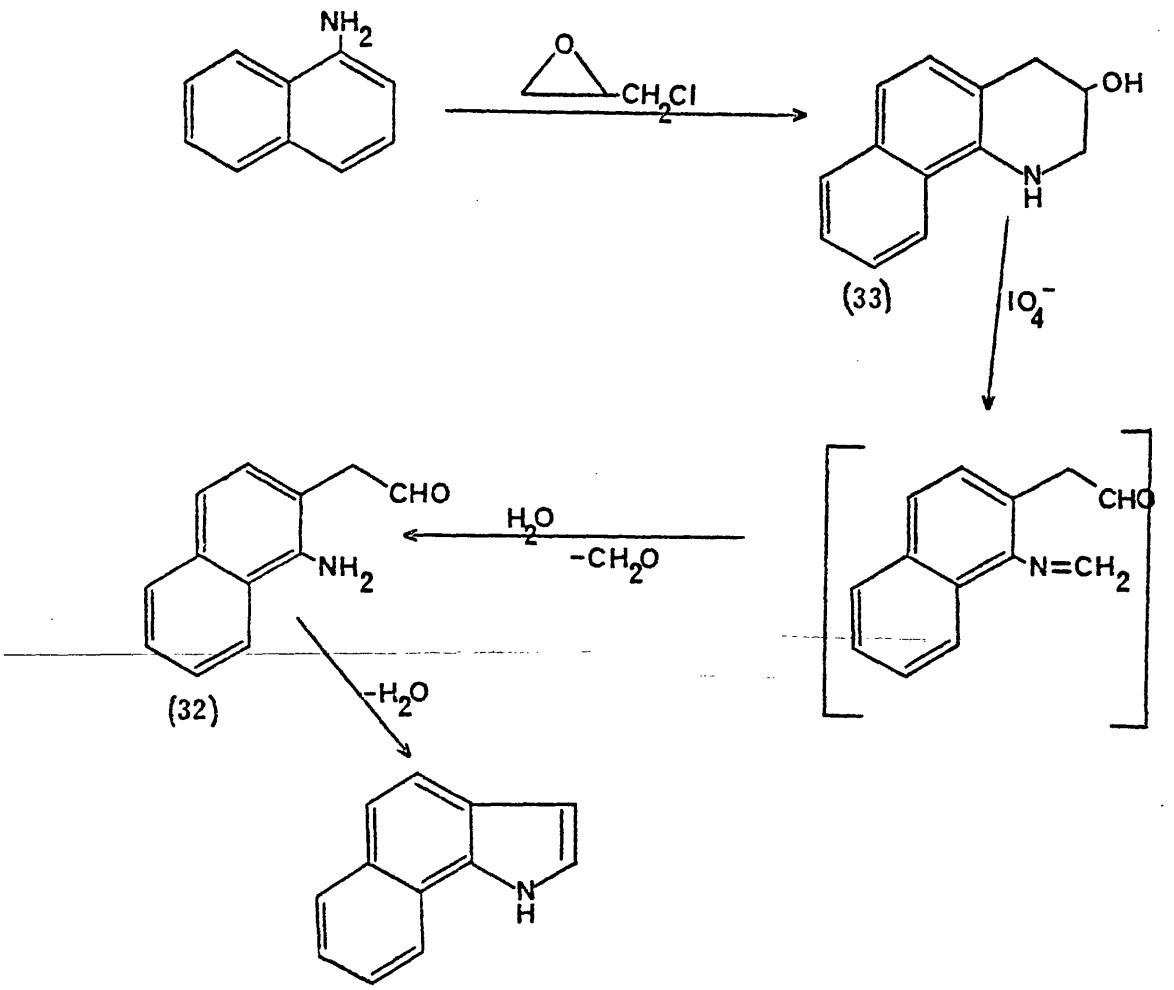
3H-BENZO [e] INDOLE

A survey of the chemical literature shows that there exist only a few synthetic methods to these compounds: two routes involve the use of the highly toxic 2-naphthylamine and for this reason were discounted. The only benzoindole which does not involve the use of this particular starting material is 1H-benzo[g]indole and various methods of preparing this compound in acceptable yields are discussed in the following section.

(ii) Synthesis of 1H-benzo [g] indole (29)

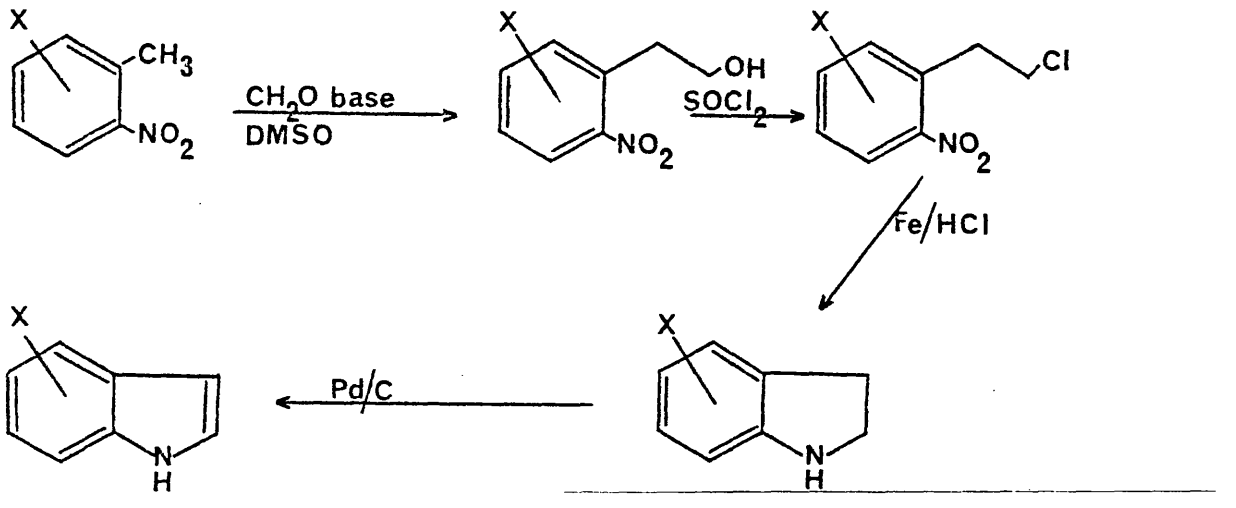
The first synthesis attempted followed work carried out by Pennington et al[39] and involves the generation of o-aminophenylacetaldehydes (32) by periodate oxidation of 3-hydroxy-1,2,3,4-tetrahydroquinolines. The initially produced aldehyde cyclises in situ to give the required indole. In our case 8-hydroxy-7,8,9,10-tetrahydro-10 H-benzo[h] quinoline

(33) being prepared by the action of epichlorohydrin on α-naphthylamine.



In operation, however, this is a laborious procedure involving steam distillation and sublimation techniques during the purification of the indole and the yield of 1H-benzo[g]indole was very disappointing. Furthermore, the amount of α naphthylamine required, together with the time needed, precluded the use of this method for the synthesis of the indole.

Bakke[40] and co-workers in Sweden have developed a synthetic route to substituted indoles using a base catalysed reaction between an o-nitrotoluene and formaldehyde in dimethylsulphoxide. The indole can be generated, subsequently, in good yield following the scheme outlined below:

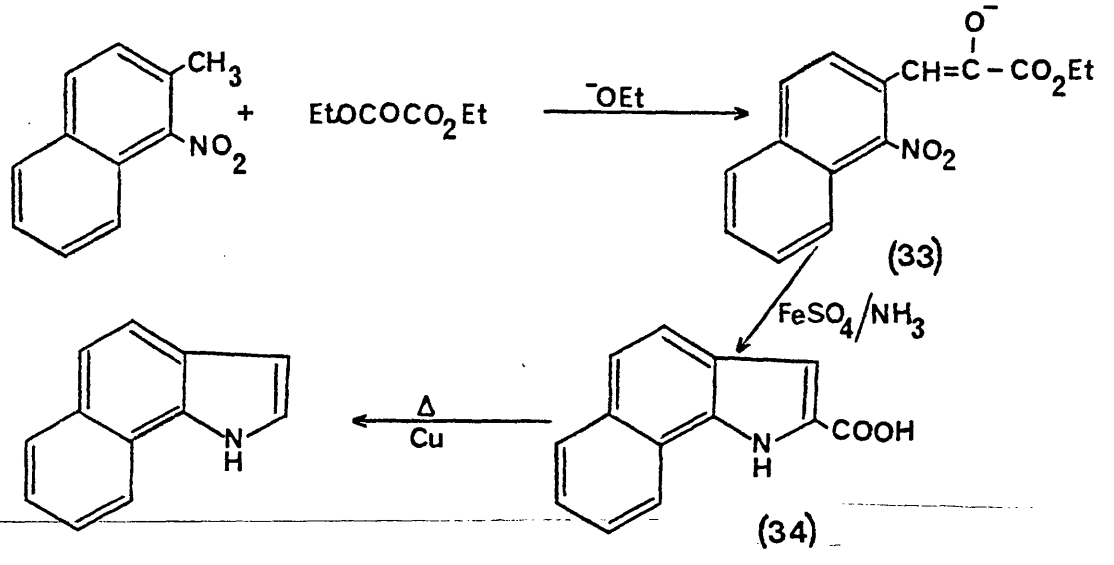


X = CH_3, OCH_3, Halogen.

Substituting 2-methyl-1-nitronaphthalene for the toluene it was decided to attempt a synthesis of 1H-benzo[g]indole in a similar manner. Using sodium ethoxide as the base, formaldehyde gas, generated by heating paraformaldehyde, was passed through a dimethylsulphoxide solution of the naphthalene. However, after chromatographic purification the only product from this reaction was a green polymeric material of high molecular weight.

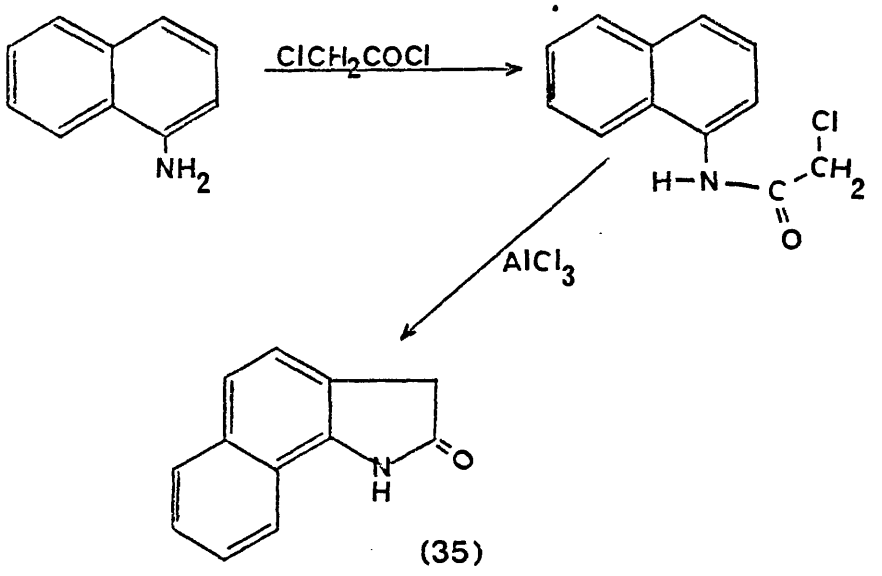
The next attempted synthesis of the benzoindole again utilized 2-methyl-1-nitronaphthalene but this time a Reissert[41] reaction was attempted. Diethyl oxalate was condensed with the naphthalene

under the influence of sodium ethoxide and the resulting pyruvate (33) ring closed to 1H-benzo[g]indole-2-carboxylic acid (34) using refluxing ferrous ammonium sulphate solution. Decarboxylation was effected by boiling in quinoline with a catalytic amount of copper powder added. This sequence is summarised below:-



The one "flaw" in this otherwise acceptable route is the decarboxylation step, the concentration of the indole acid must be kept low in order to achieve maximum yields and this introduced a very large time element. Indeed, this is sufficiently important to rule out this procedure since a relatively large amount of the benzoindole was required.

Despite conflicting reports[42,43] an attempt was made to prepare 1H-benzo[g]indole by the reduction of 6,7-benzoxindole (35). The oxindole was easily produced, and in good yield, by reacting chloroacetylchloride with α-naphthylamine and ring closing the product using aluminium chloride in nitrobenzene:



(35)

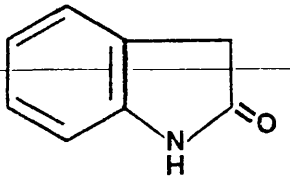
It was hoped that the oxindole would form the corresponding indoline on reduction, which would then afford the indole by catalytic dehydrogenation.[44]

The attempted reduction of 6,7-benzoxindole was carried out using two reagents; firstly lithium aluminium hydride and secondly diborane, prepared by the action of boron trifluoride etherate on sodium borohydride in diglyme. In both cases, however, a mixture of starting material and the indoline was produced as a resinous gum. Mass spectral analysis revealed peaks at m/e 183 and 169 corresponding to the oxindole and indoline respectively, and the infrared spectrum contained an amide carbonyl stretching band at 1680cm^{-1}, typical of an oxindole. This gum, in ether, was extracted with dilute hydrochloric acid to yield, on basification and re-extraction, yet another brown gum, but now the infrared showed no evidence of an amide carbonyl group and additionally the two amide N-H stretching bands at 3220cm^{-1} and 3250cm^{-1} present in the original spectrum had also disappeared. Instead, a broad secondary amine band 3360cm^{-1} was

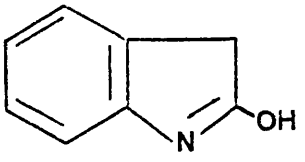
prominent. On this evidence we assume that some of the desired benzoindoline was formed, but the crude yield so obtained was poor and purification procedures were unproductive.

A great deal or work has been undertaken concerning the reduction of oxindoles, and over a period of more than a century a large number of reagents capable of reducing various oxindoles, have been accumulated.

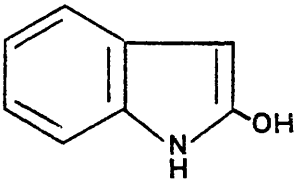
The structure of oxindole is generally regarded as the lactam (36) of o-aminophenylacetic acid. The two enol tautomers (37) and (38) also represent possible formulations.



(36)

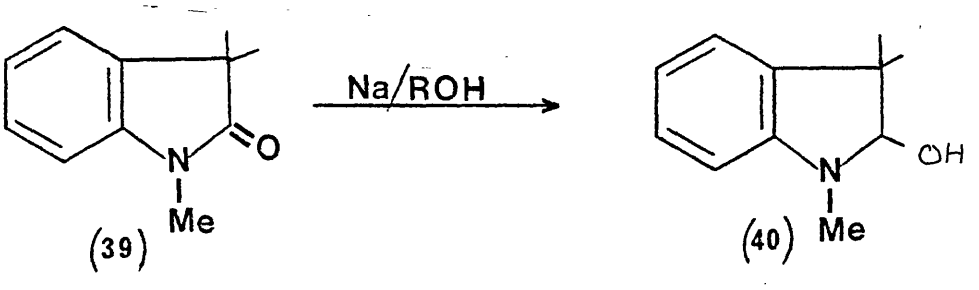


(37)



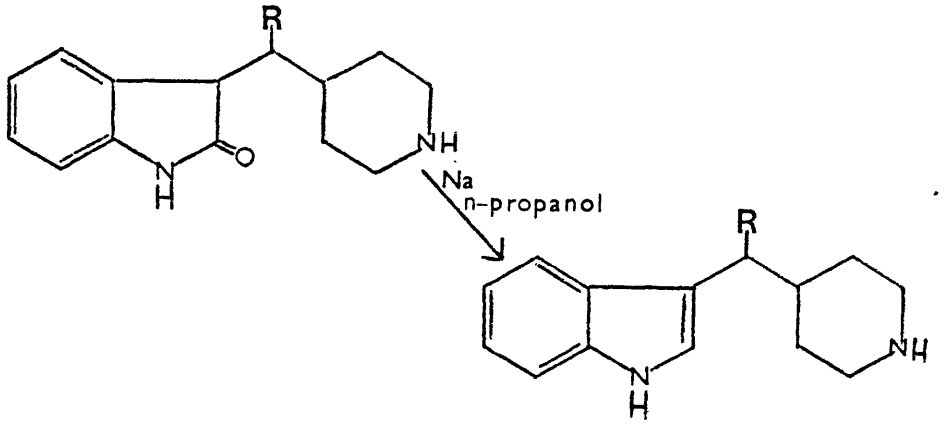
(38)

However, spectral data of 1-methyl and 1,3,3-trimethyloxindole are very similar to that of oxindole[45] indicating that the lactam structure is predominant. One of the first documented methods of reducing this compound was described by Baeyer[46], it was, however, very tedious and reduction was carried out by passing oxindole vapour over heated zinc. Later, lithium aluminium hydride was used to effect reduction, with a certain amount of success, although this seemed ineffective against oxindoles unsubstituted at the one position[47]. Sodium in alcohol has also been reported as effective in reducing oxindole derivatives, although an earlier publication[48] suggests that successful reduction of the amide carbonyl group requires a highly alkylated oxindole. Thus 1,3,3-trimethyloxindole (39) is reduced by sodium in alcohol to the corresponding indolinol (40).



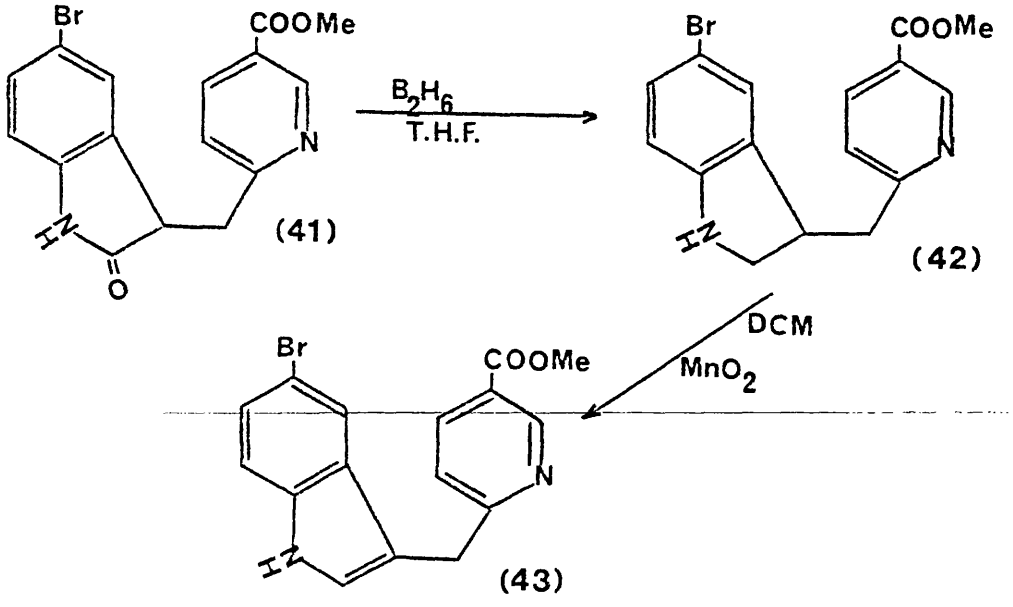
(39) (40)

Since then, sodium in n-propanol has been reported[49] to reduce monosubstituted oxindoles to indoles, an example is cited below:

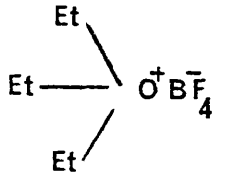


Work carried out by Brown et al[50] showed that diborane in tetrahydrofuran could be used, with success, to reduce 1^0,2^0 and 3^0 amides. Thus it was not long, before this reagent was employed in the reduction of oxindoles.

Julia et al[51] reduced the oxindole (41) in good yields to the indoline (42) which was subsequently dehydrogenated to the indole (43).



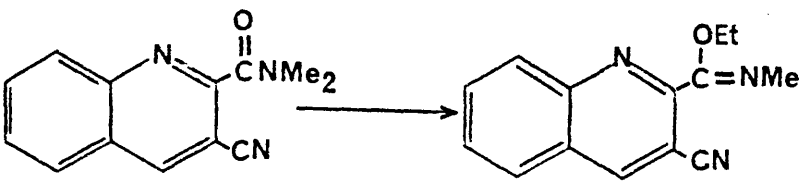
Another reagent which is used in the conversion of oxindoles to indoles is Meerwein's reagent[52], or triethyloxonium tetrafluoroborate (44).



(44)

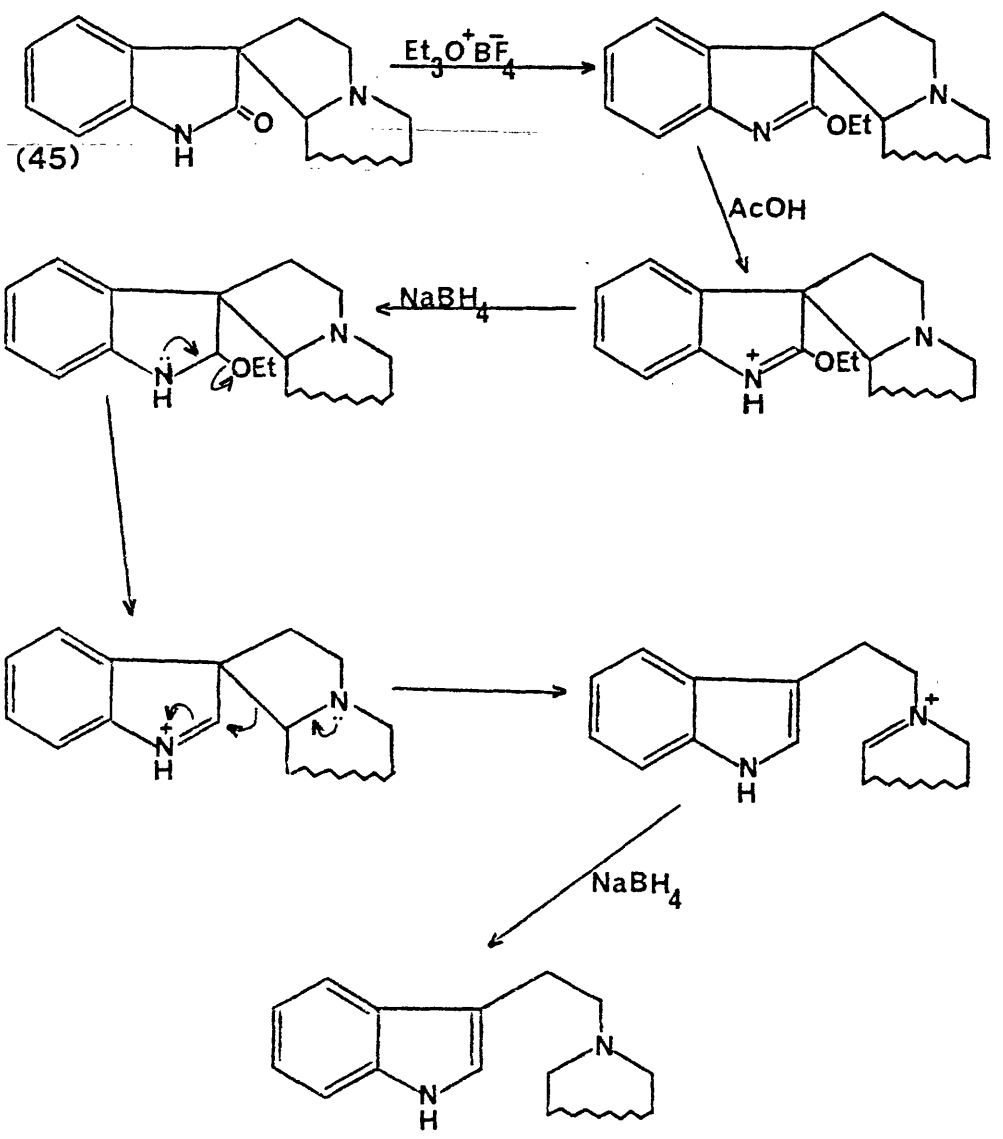
This reagent appears to react with amides to form imine ethers[53].

e.g.,



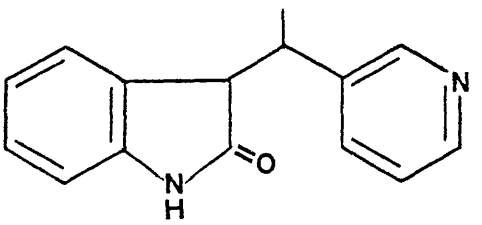
Iminium salts may be reduced to the corresponding amines.

This was employed by Aimi et al[54] in the reduction of the oxindole alkaloid (45).



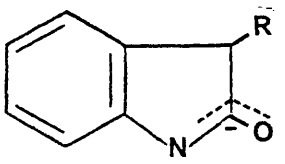
It has been found, however, that certain oxindoles defy reduction using any of the reagents mentioned.

Kilminster[55] came up against this problem whilst attempting to reduce compounds of the type (46).



(46)

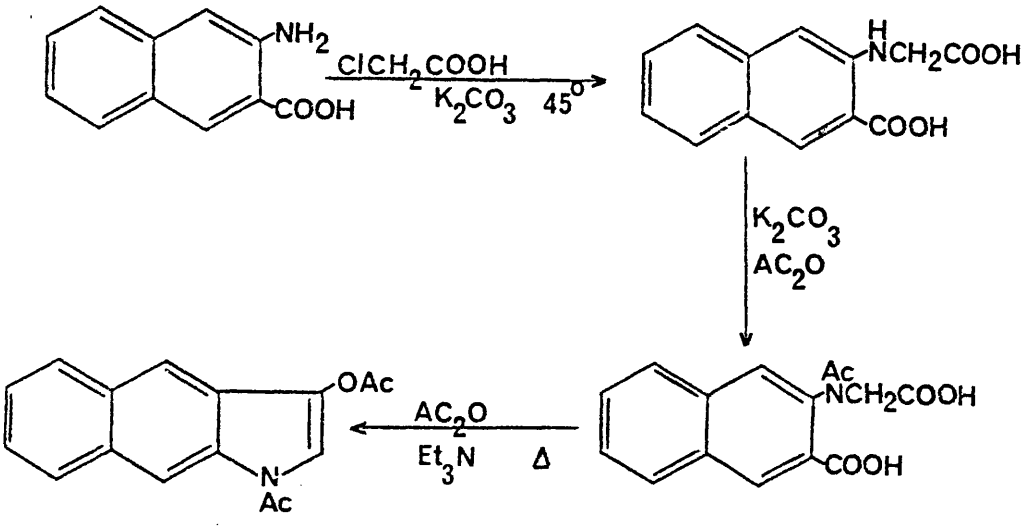
Either starting material was returned, or if strong conditions used, i.e., refluxing lithium aluminium hydride in tetrahydrofuran then multicomponent tars were afforded. This, presumably could be due to the formation of the anion (47) if the N-H group is unsubstituted.



(47)

The vast majority of synthetic routes available to indole can, in theory, be modified to the preparation of benzoindoles, but in practice their adoption produced difficulties due either to the expense or the toxicity of the necessary starting materials. Work carried out by a number of researchers[56,57] has shown that indole and its derivatives can be prepared by an acid or base catalysed dehydration of 3-hydroxyindolines. The author considered the possibility of preparing 3-hydroxybenzo[f]indoline from 1,3-diacetylbenzo[f]indoxyl (48), produced via the scheme

outlined below:

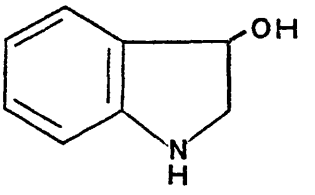


(48)

Since the starting material, 3-amino-2-naphthoic acid, was rather expensive, it was thought wise to assess this synthesis initially using 1,3-diacetylindoxyl, which was made in an identical manner but starting from anthranilic acid.

With the starting material in hand the indoxyl was warmed in an aqueous solution of sodium sulphite to produce 1-acetylindoxyl[58] as a light brown solid. After purification this compound was dissolved in ethanol and excess sodium borohydride added whilst the reaction was kept cold (0-5^{0}C). After stirring for half an hour the solvent was removed, under high vacuum, at about 30^{0}C and the solid residue extracted with chloroform. After removal of the solvent and purification, a light brown solid was formed which could not be stored for longer than a few hours; since decomposition to a brown tar occured. It was, however, tentatively assigned the structure shown below (49), since infrared data showed two bands at υ 3490 and 3280cm^{-1} indicating the presence

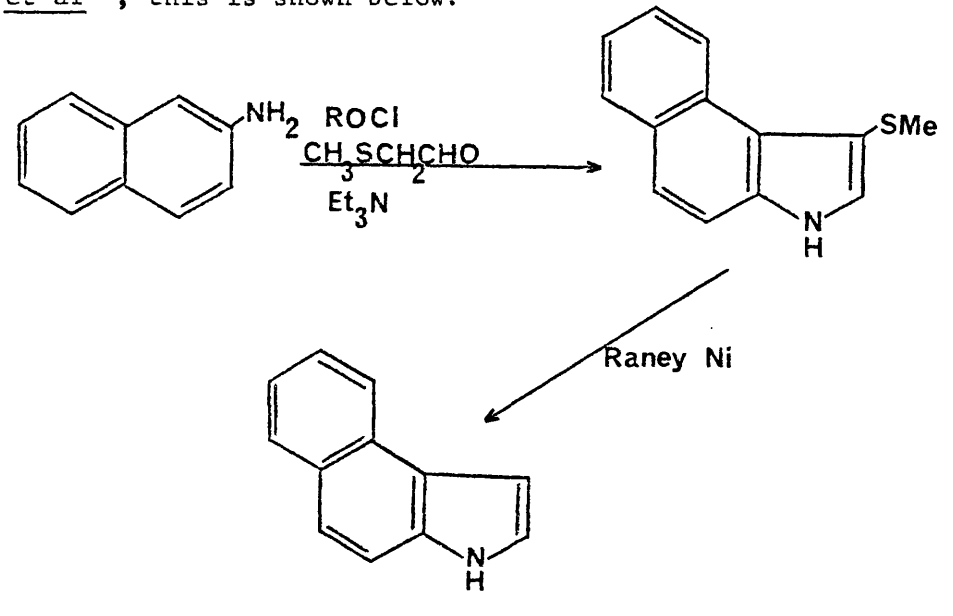
of a hydroxyl function as well as the amine stretching frequency. The absence of a carbonyl band was also noted. Mass spectrum data gave peaks at m/e 135 and 117; again indicating the possible formation of 3-hydroxyindoline.



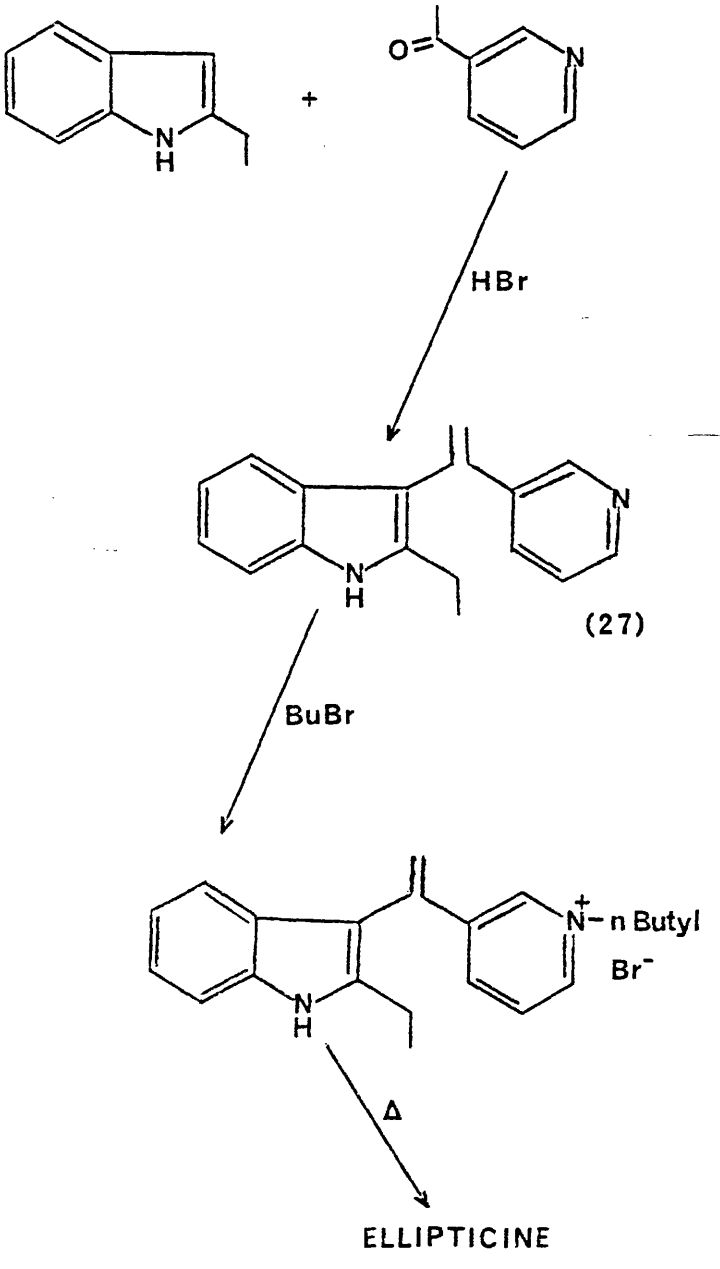
(49)

This compound was quickly taken up in dry ether and reacted with dry hydrogen chloride, but on working up, however, a 'sticky' brown gum had formed and from this only a small amount of indole was produced. The residue appeared to be mainly polymeric in nature (see below) but even when acidic conditions were avoided in attempts to effect dehydration of the indolinol little progress was made.

At this stage it seemed as if the problem of benzoellipticine synthesis hinged upon a search for an efficient preparation of simple starting materials; although some time after this work was complete an efficient synthesis of benzoindoles was achieved by Gassman et al[59], this is shown below:-

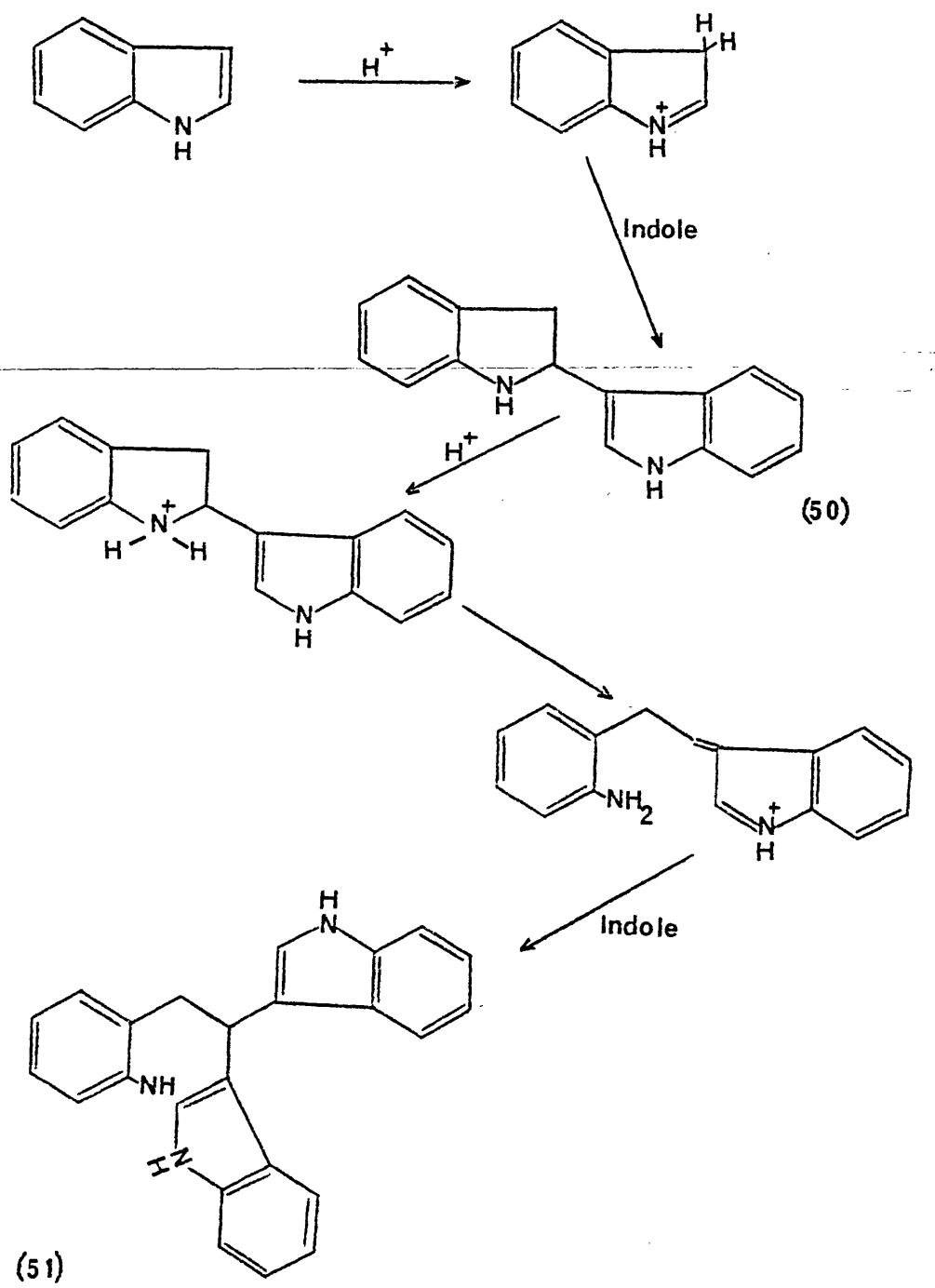


In the search for efficient methods of producing starting materials the author decided to follow some synthetic studies carried out by Bergmann and Carlsson[60] in the indole series. This group had successively prepared ellipticine in excellent yield starting from the easily accessible 2-ethylindole, as shown below:

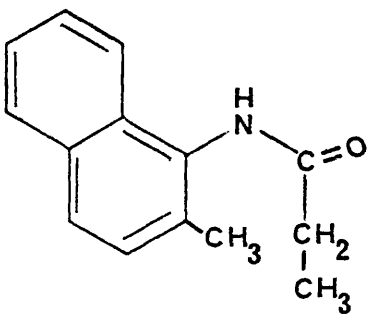


Since the indole is substituted in the C-2 position it is not susceptible to acid dimerisation (50) or trimerisation (51) and the condensation between 2-ethylindole and 3-acetylpyridine can be carried out in strong acid, and the product (27) isolated in excellent yield.

Acid catalysed polymerisation of indole



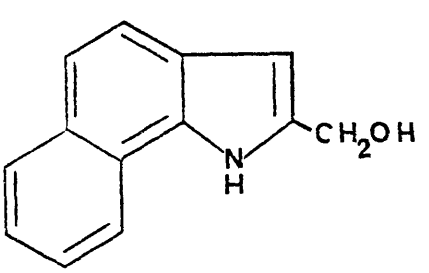
The preparation of the benzo derivative of 2-ethylindole should not prove too difficult since 2-alkylindoles are easily produced and in good yields following the well documented Madelung method[61]. The starting material 2-methyl-1-nitronaphthalene which is difficult to make and expensive to buy, was reduced to the corresponding amino compound in good yield using iron filings and hydrochloric acid. This, when reacted with proprionyl chloride gave the amide (51).



(51)

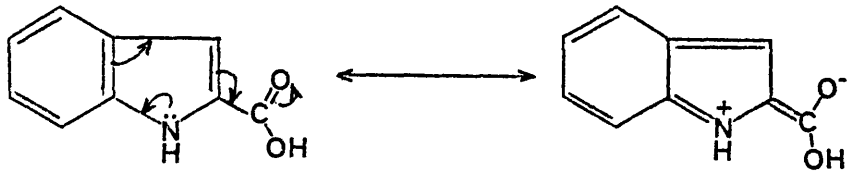
The ring closure was carried out using sodium amide in the absence of any solvent. On hydrolysis and extraction however, a dark oil was obtained which became resinous on any attempt at distillation. The conditions used in this reaction were probably too harsh and that if more starting material was available it may have been more profitable to carry this reaction out in a solvent such as N,N-diethylaniline[62].

The success of the condensation achieved by the Swedish group 'sparked' off two speculative attempts at condensing 3-acetylpyridine with, firstly, benzo [g] indole-2-carboxylic acid and secondly with 2-hydroxymethylbenzo [g] indole (52), made by the lithium aluminium hydride reduction of the acid in tetrahydrofuran.

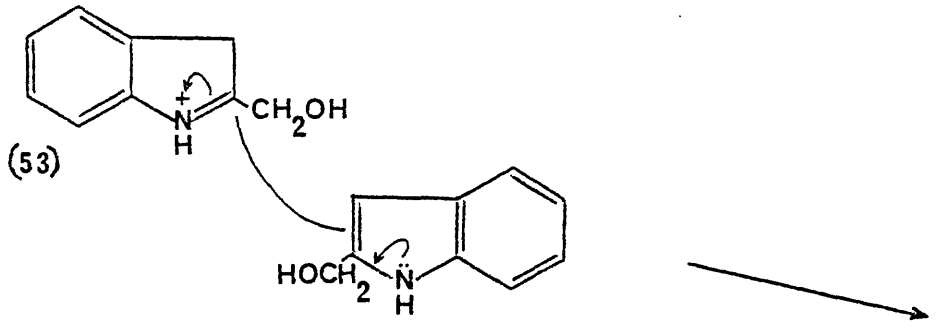


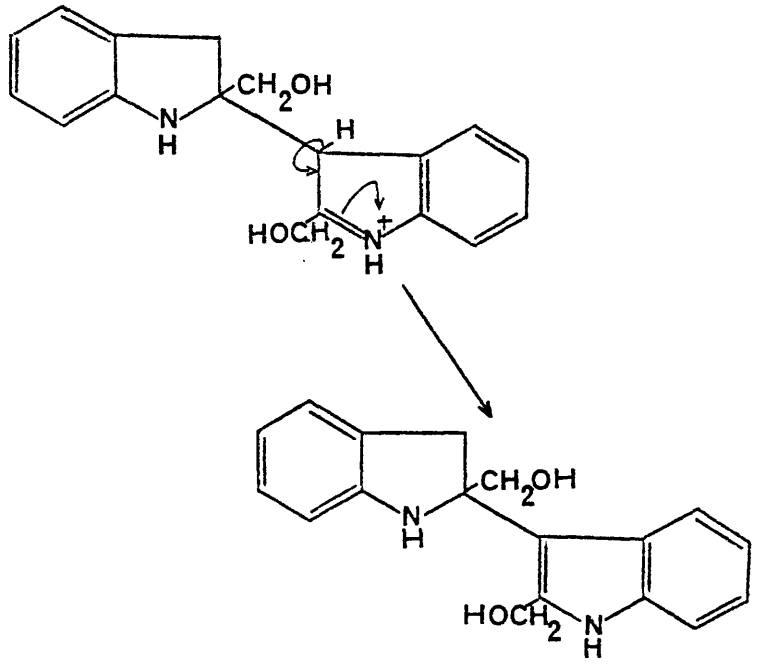
(52)

The carboxylic acid failed to combine with 3-acetylpyridine and starting material was returned, probably due to the reduced nucleophilic character of the indole C-3 position relative to indole itself.



This situation does not arise in the alcohol but disappointingly a reaction between it and 3-acetylpyridine gave a dark resin. Extraction with dilute hydrochloric acid returned the vast majority of 3-acetylpyridine, the remaining gum was neither pyridine nor starting alcohol and chromatographic techniques for purification were unproductive. It may be possible that some dimer (54) had been formed by nucleophilic attack of the alcohol on the cation (53), although no evidence to suggest this was found.



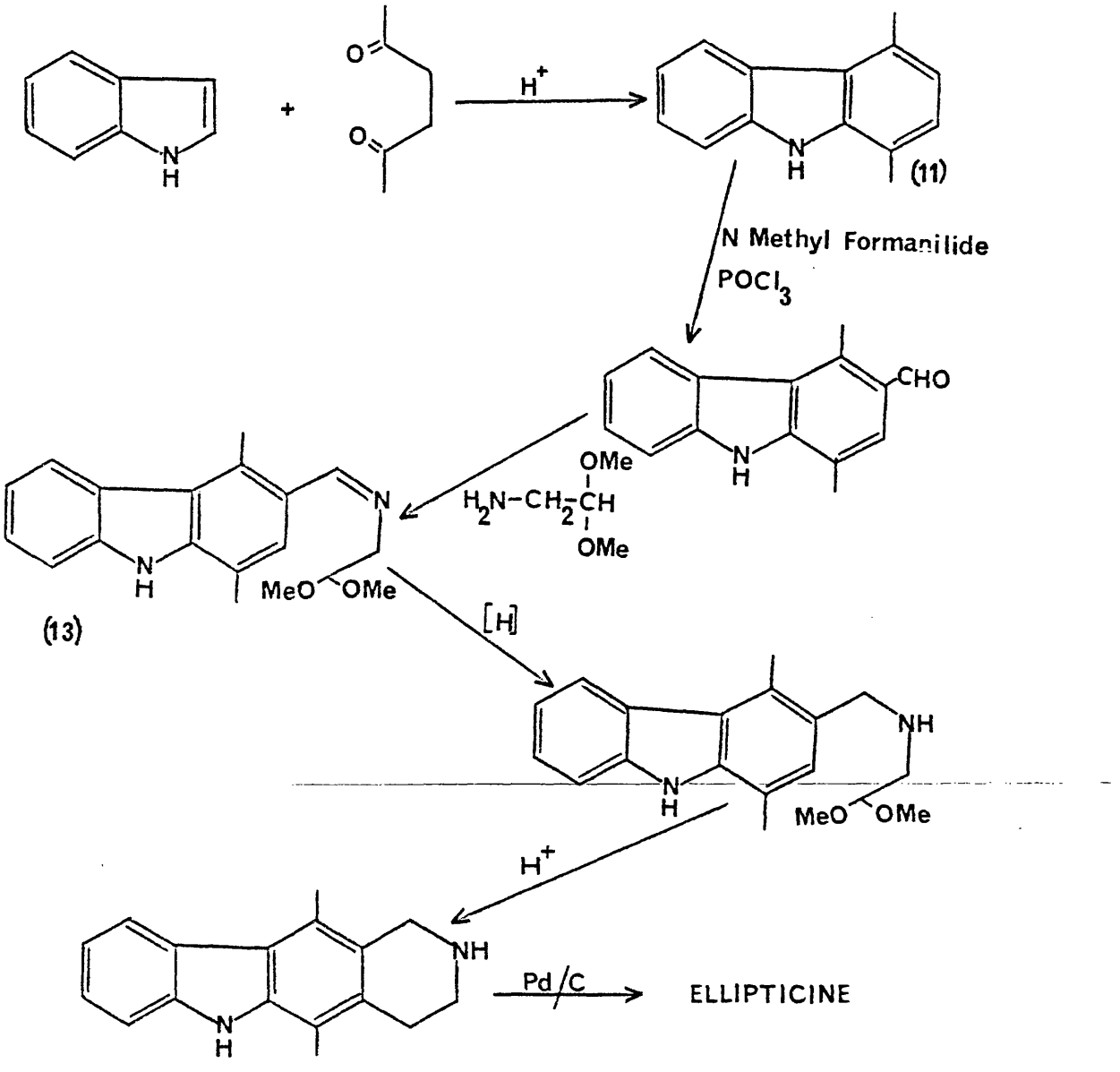


(54)

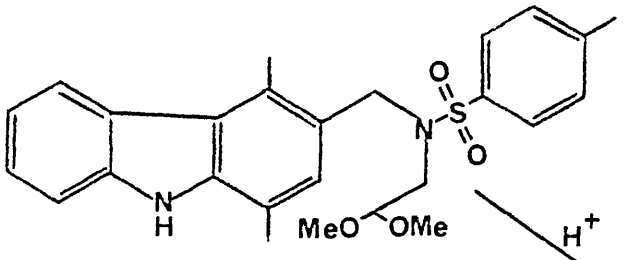
After this final attempt at a benzoellipticine synthesis from indoles, the emphasis was turned to preparations employing other routes which are discussed in the sequel.

Preparation of Benzocarbazole

Having found great difficulty in producing the necessary amount of benzoindole (29) for the Grignard route (page 24) from any of the attempted syntheses just described it was decided to turn our attention to the preparation of one of the three benzoellipticines via the established Cranwell and Saxton method[26,27] shown below:



In the original, 1,4-dimethylcarbazole (11) was formylated using a Vilsmeir procedure then dimethoxyethylamine employed to construct the remaining ring of the tetracyclic structure in a Pomeranz-Fritzch synthesis. As mentioned previously, the final acid ring closure of this route has been modified on two occasions, firstly by Dalton[30] who employed phosphoric acid on the azomethine (13) and secondly by Guthrie[31] who developed an acid ring closure of the N-p-toluenesulphonyl derivative (16).

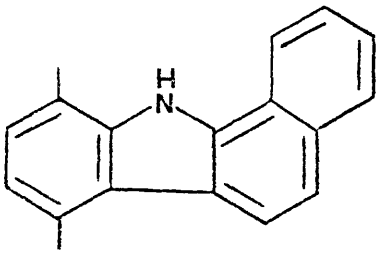


ELLIPTICINE

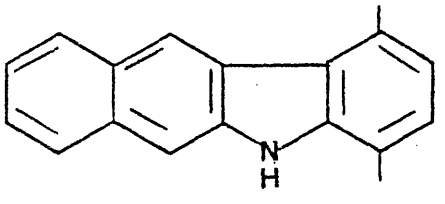
(16)

The initial step in the Cranwell and Saxton scheme produces the carbazole (11) from an acid condensation of indole with hexane-2,5-dione but in the case of the three benzocarbazoles required for our purposes a more expeditious route, at least on paper, would involve the simple indolisation reactions of naphthalene derivatives.

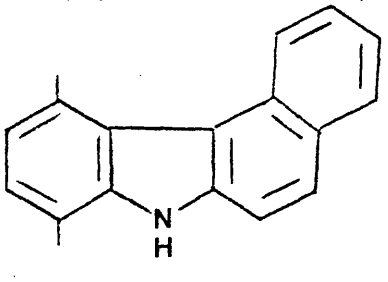
However, it soon became apparent that we were once again limited to the synthesis of only one of the three possible benzocarbazoles; again lack of availability of starting material and toxicity limited us in our preparative attempts.



7, 10-Dimethyl-11H-benzo[a]carbazole



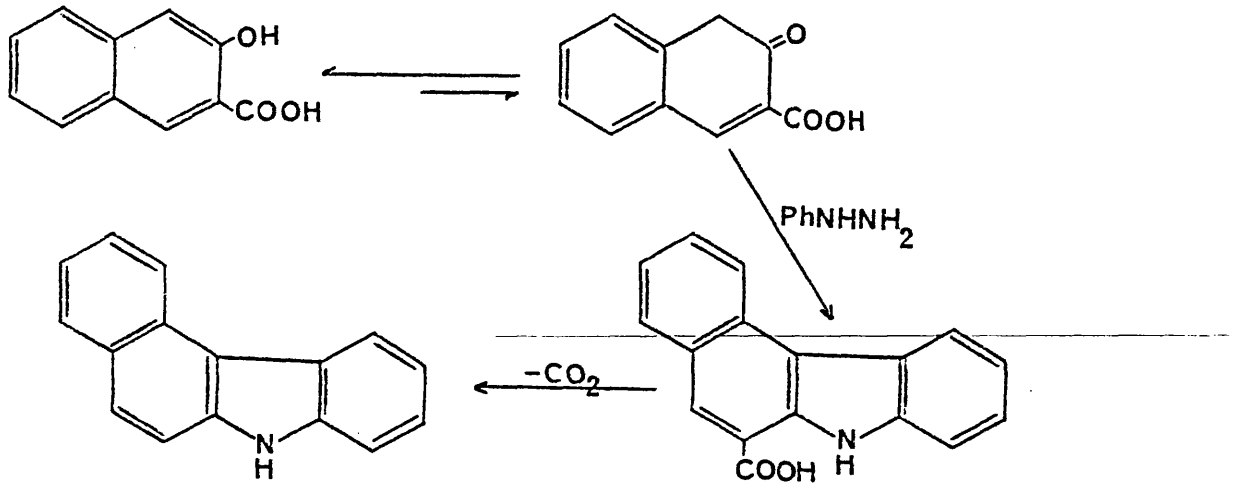
1,4-Dimethyl-5H-benzo[b]carbazole



8,11-Dimethyl-7H-benzo[c]carbazole

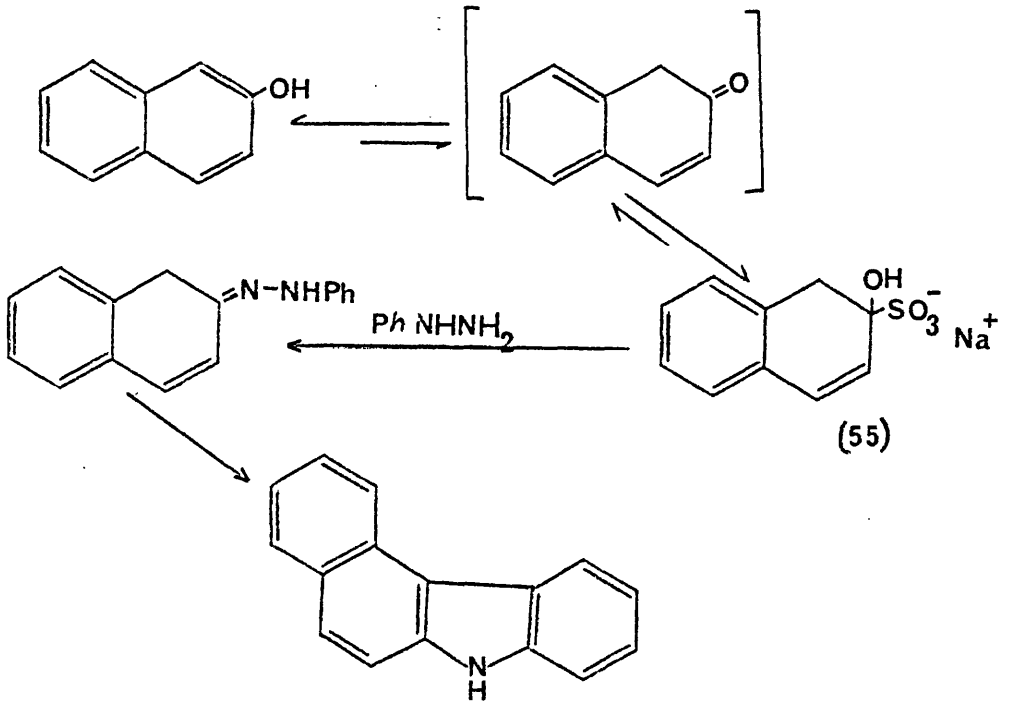
Another approach considered at this time was one which utilized the Bucherer method[63]. Thus the two angular benzocarbazoles might be available in this way and our speculations along these lines are now considered.

Schopff[64] found that certain phenols appear to react in the keto form when heated with phenylhydrazine affording carbazole derivatives, as shown below:-



This procedure was modified by Bucherer[65] and by reacting a suitable phenol with phenylhydrazine in the presence of bisulphite, was able to prepare various benzocarbazoles in good yields. Bucherer[66] also found it possible to convert certain aromatic amines to phenols by refluxing in aqueous bisulphite. Thus amines could be used in place of phenols and benzocarbazoles still produced. The mechanism is thought to be one of nucleophilic attack by bisulphite on the carbonyl carbon. The addition complex (55) is then formed only slowly, but once formed, is stable in aqueous solution; in fact so much so that addition of rather

strong acid is required to regenerate the phenol:

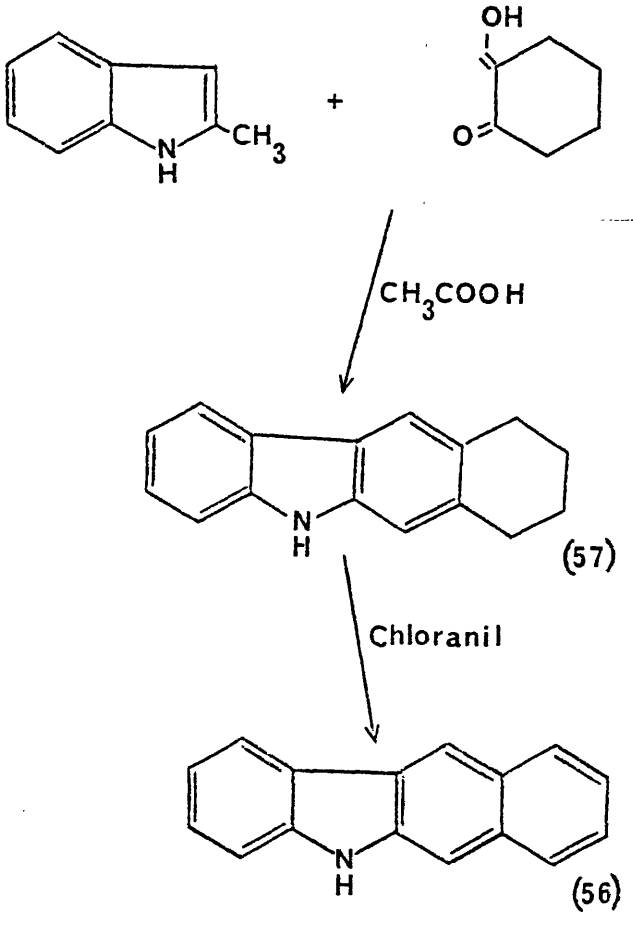


(55)

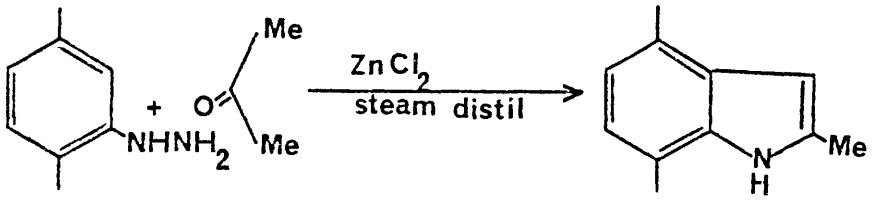
In our case the hydrazine required was p-xylylhydrazine and this was prepared from 2,5-dimethylaniline by the diazotization and stannous chloride reduction of the corresponding diazonium salt[67].

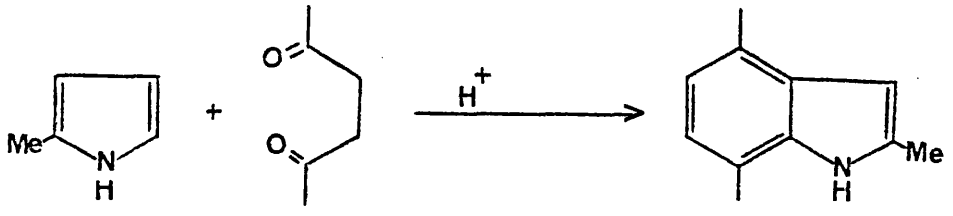
Once prepared, the hydrazine was then reacted with firstly 2-naphthol and secondly 1-naphthol according to the Bucherer method. In both cases, however, high melting crystalline salts were formed which could not be converted to the free carbazoles by treatment with a variety of strong acids. Mass spectrometric data of the acid treated salts indicated the presence of free benzocarbazoles but infrared spectra showed bands at about υ 1075cm^{-1} indicating the possible presence of a sulphite group. Since these salts are probably highly involatile they may not be apparent in the mass spectrum.

Frustrated again in our synthetic aims the possibility of preparing the linear benzocarbazole was visualised using a method developed by Johnson et al [68] for the synthesis of the desmethyl analogue (56). Here 2-methylindole was condensed with 2-hydroxymethylenecyclohexanone in strong acid. The resulting 7,8,9,10-tetrahydro-5H-benzo[b]carbazole (57) was dehydrogenated to the fully aromatic benzocarbazole in approximately 36% yield using a high potential quinone as an oxidant:



For our purposes 2,4,7-trimethylindole is required but only two documented routes exist to this compound and both these give poor yields. The first involves zinc chloride as a catalyst in a Fischer reaction[69] and the second a condensation between 2-methylpyrrole (58) and hexane-2,5-dione[70]; both these routes are outlined below:

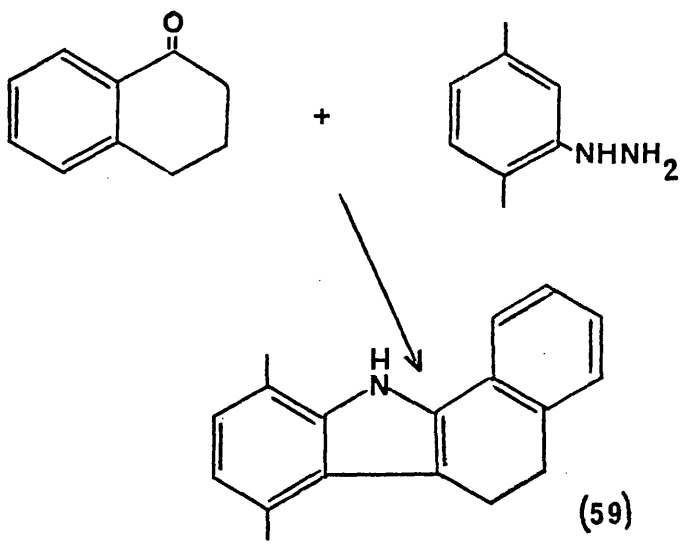




Synthesis was attempted however, using an indolisation step employing, firstly, boron trifluoride etherate and secondly polyphosphoric acid. These attempts failed although it seems from mass spectrometric analysis of the tarry products some of the desired indole was formed, but only in extremely low yield.

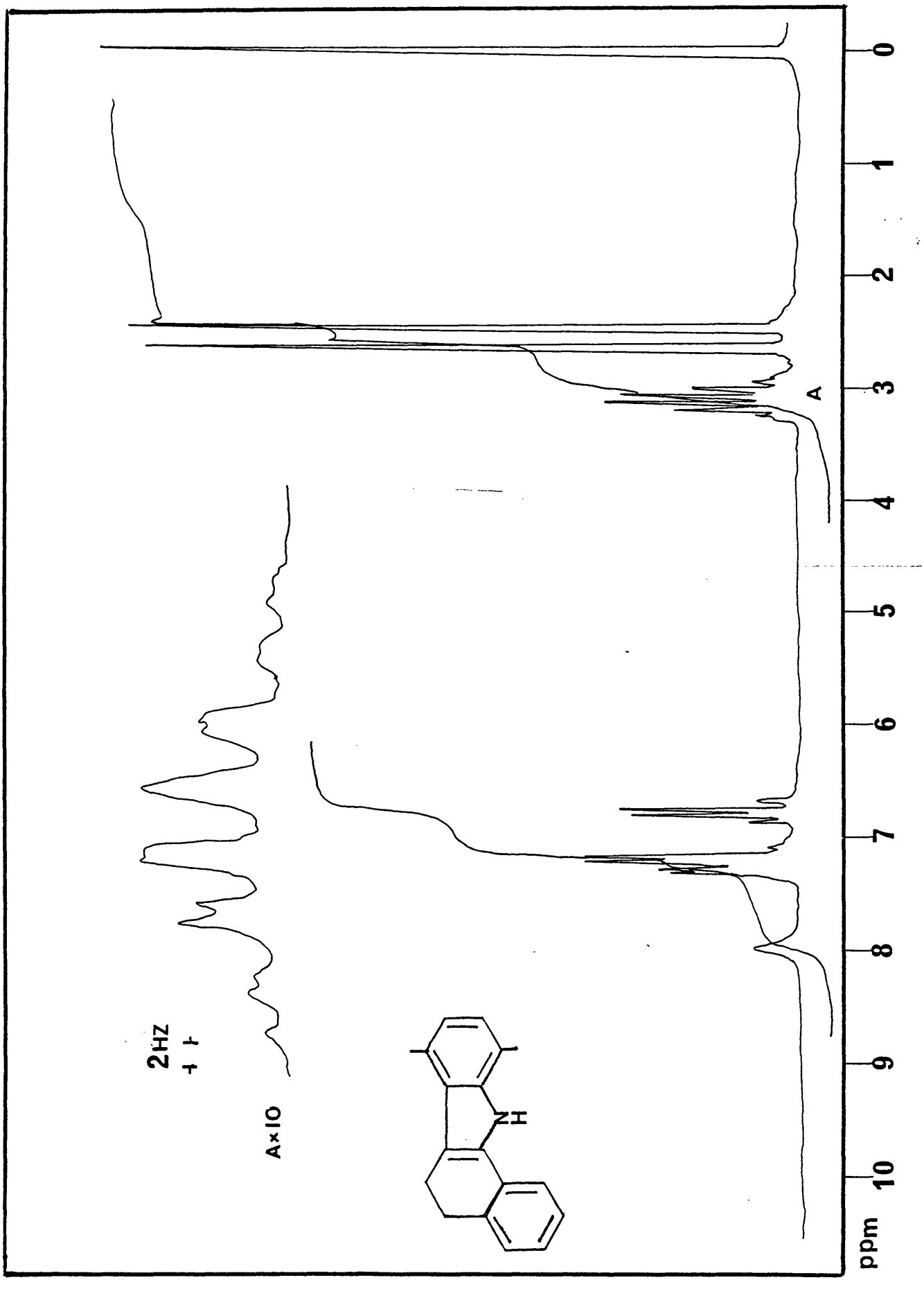
After these disappointing results it was decided to turn our attention to the synthesis of the benzocarbazoles by the Fischer indole method[71,72], to avoid the use of large quantities of α-and β-naphthylamines. It was thought that both the angular benzocarbazoles could be prepared by condensing 1- and 2-tetralones with p-xylylhydrazine. However, the expense and nature of 2-tetralone made this unsuitable for use on the large scale.

1-tetralone, however, was easily obtained, and the treatment of this with p-xylylhydrazine under various conditions (dilute hydrochloric acid, dilute sulphuric acid and boron trifluoride etherate) produced the desired 5,6-dihydro-7,10-dimethyl-11H-benzo [a]carbazole (59) in excellent yield. This dihydrobenzocarbazole was easily authenticated from an analysis of its ^{1}H nuclear magnetic resonance spectrum (shown overleaf) which showed a multiplet centred at 3.1ppm due to the signals of the two sets of non-equivalent methylene protons with a coupling of 15.5Hz. An AB system also shows up clearly centred at 6.8ppm due to the non-equivalent protons at C-8 and C-9, with a coupling constant of 10Hz. As is common with most carbazoles the hydrogen atom on the nitrogen did not exchange with deuterium.

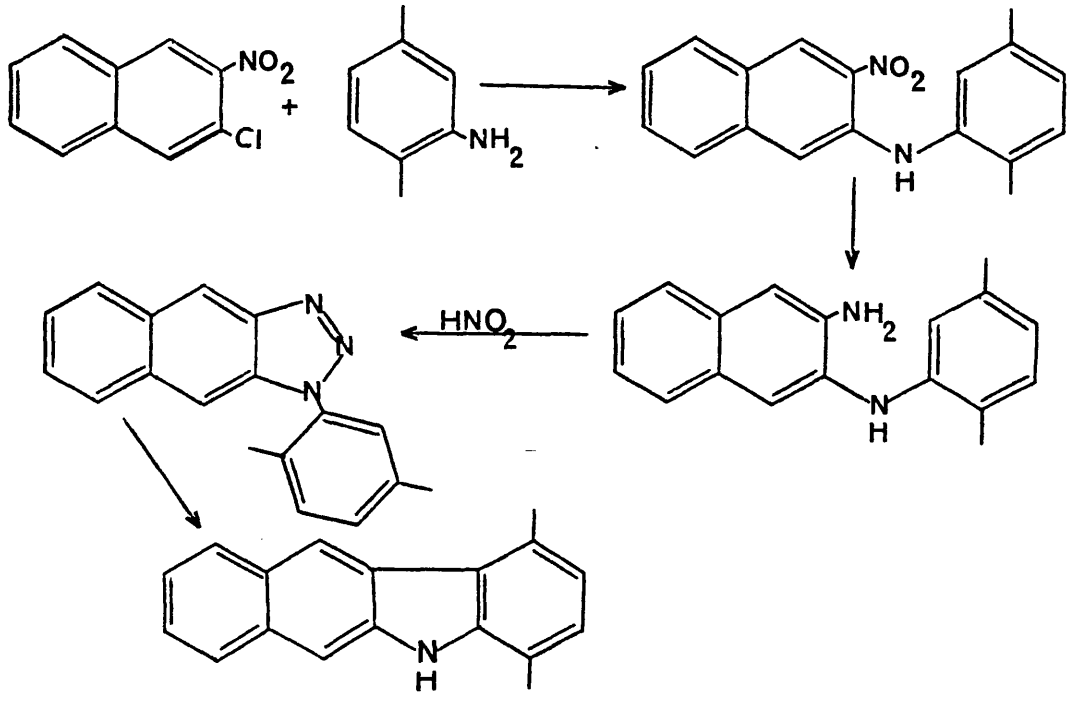


(59)

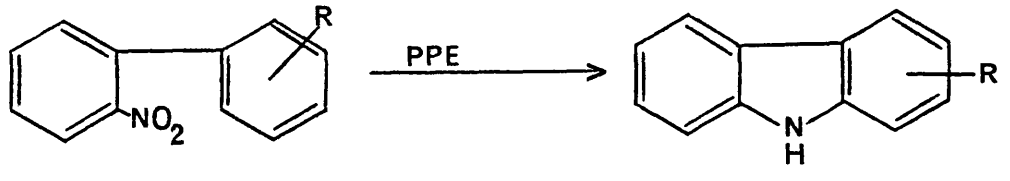
Thus with one isomer, or at least its dihydroderivative, "in the bag" our thoughts centred upon the remaining two but attempts at preparing the remaining benzocarbazoles by the modification of literature methods were discounted due to the lack of general availability of the appropriate ortho disubstituted naphthalene compounds.

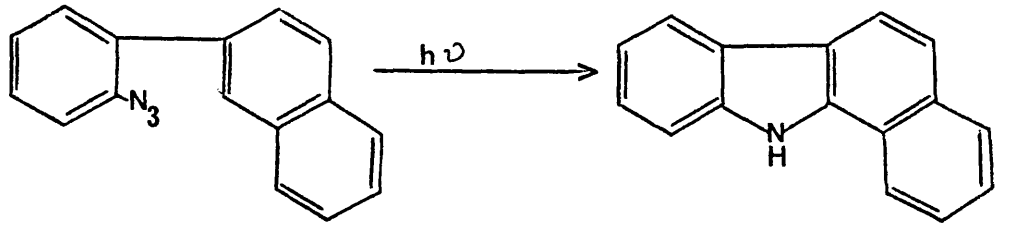

2HZ
A×10
A
N
H
0
1
2
3
4
5
6
7
8
9
10
ppm

A modification of the Graebe-Ullman synthesis by Plant et al[73] (outlined below) for instance, requires the preparation of 2-chloro-3-nitronaphthalene or an equivalent. Such a compound is not commercially available and its synthesis is extremely tedious.

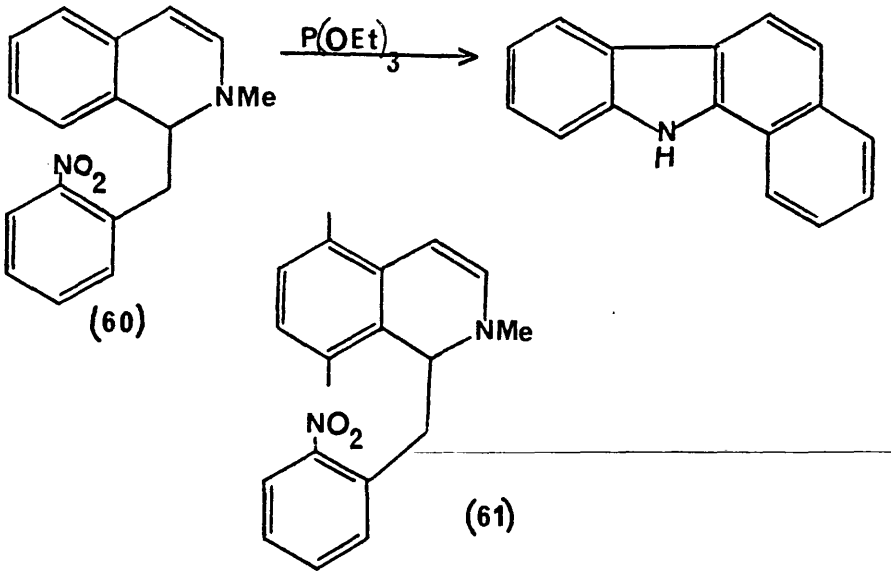


Preparations of many carbazoles and benzocarbazoles have been carried out by employing the reactions of electron deficient nitrenes, either from nitro[74] compounds or azides[75]. Two examples are given below:





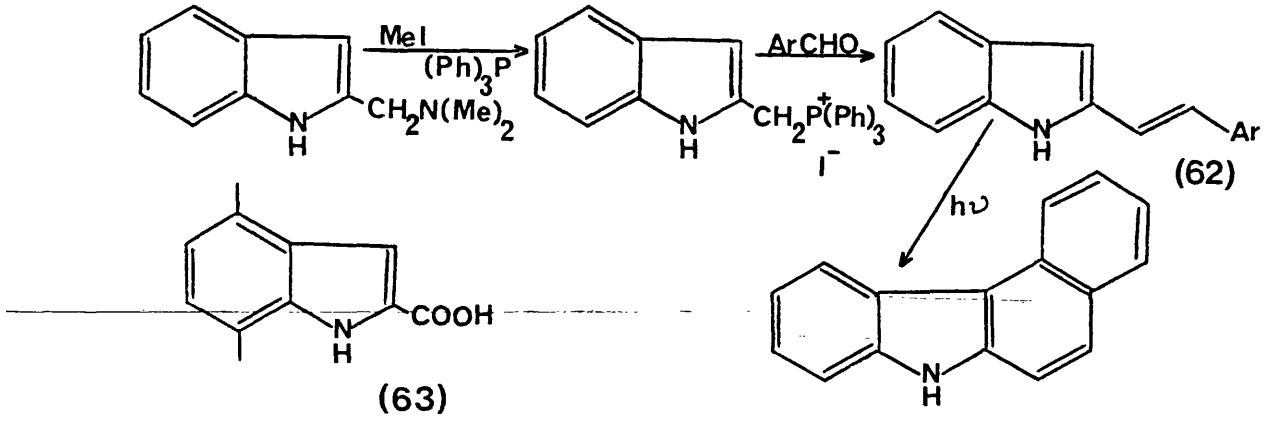
One novel synthesis of benzo[a]carbazole, also employing a nitrene as the intermediate was carried out by Kametani et al[76] and involved the reductive cyclisation of 1-(2-nitrobenzyl)-isoquinoline (60) using triethyl phosphite. Thus we might envisage the sequence shown, but clearly the required substrate (61) is not readily available.



These particular "last steps" all work in good yield but the syntheses overall have the disadvantage of giving low productivity since often the starting materials are inaccessible.

One particular reaction sequence which was initially considered by the author was a preparation of benzo[c] carbazole by a photochemical ring closure of 1-(2-indolyl)-2-arylethylene (62). On further consideration, however, this was discarded since the final photochemical step would have been difficult to scale up, to afford the amount of benzocarbazole required in a reasonable period of time.

De Silva and Snieckus[77] pioneered this photochemical process which works in 70% yield. The whole process, which is outlined below, is lengthy but the starting materials are easily accessible. Modifications to our purposes could have been carried out by replacing indole-2-carboxylic acid by 4,6-dimethylindole-2-carboxylic acid (63); which hopefully could have been prepared by employing indolisation conditions between p-xylylhydrazine and ethylpyruvate. This synthesis represents a facile entry into the benzocarbazole and pyridocarbazole series.



Inevitably, much time had been spent on unyielding chemistry and since our aim, to provide pharmacologists with compounds to test, had not been fulfilled, we were placed under pressure to complete the synthesis of at least one of the targets. Thus we began the sequence which we anticipated would lead to 7,8-benzoellipticine.

Formylation of Benzo [a] carbazoles

The initial formylation reaction was carried out on the dihydrobenzocarbazole, since the possibility of formylation at positions other than the required C-8 site of the fully aromatic benzocarbazole had been born in mind.

With the necessary amount of dihydrobenzo[a]carbazole in hand the Cranwell and Saxton route was commenced.

Formylation was attempted using the standard conditions of phosphoryl chloride and N-methylformanilide in o-dichlorobenzene. On completion the solvent was removed by steam distillation and the crude product purified, firstly by Soxhlet extraction and then crystallisation from toluene. However, after several attempted crystallisations only a bright yellow amorphous solid was obtained, which had a rather indefinite melting point 198 - 204^{0}C. Identification of this product proved rather difficult since the ^{1}H nuclear magnetic resonance spectrum showed all the peaks to be very broad and no amount of crystallisation or chromatography would improve their resolution. Mass spectrometric data for this compound was consistent with the formation of a formylated product. Peaks at m/e 275, 273 and 244 suggested aromatisation in the instrument followed by loss of a formyl radical.

The infrared spectrum showed peaks at ν 3,300, 1,670, 1620, and 1,610cm^{-1} which indicated the possibility of a conjugated cyclic imine. The ultraviolet spectrum showed maxima at λ 260br, 300 and 340nm. As mentioned before, very little detail could be extracted from the ^{1}H nuclear magnetic resonance spectrum except that the aliphatic region was very complex and in the aromatic region the AB system at C-8, C-9, exhibited by the starting compound was almost indistinguishable. After much chromatographic work, which was largely unproductive, we concluded that since the CH and N analysis and mass spectrum indicated that we had a strong likelihood of the correct structure, it was the presence of paramagnetic ions

which were causing the distortion of the ^{1}H nuclear magnetic resonance sprectrum. Thus the aromatisation of the presumed carbonyl derivative was undertaken in the hope that this product might prove more easy to characterise.

Attempted aromatisation initially with palladium on charcoal in benzene and then in toluene gave only what appeared to be starting material. When p-cymeme was used as the solvent and the product isolated, spectroscopic data showed the problem to be even more perplexing. The ^{1}H nuclear magnetic resonance spectrum was even more complex and in the mass spectrum peaks at m/e 293, 279, 259 and 243 were exhibited.

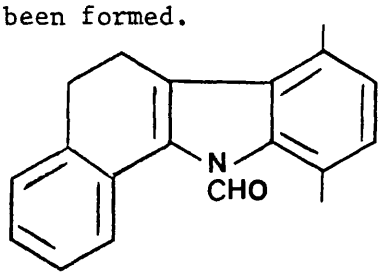
The use of such a high boiling solvent had appeared to "trigger off" a series of untoward reactions. A final attempt at dehydrogenation was carried out, using 2,3-dicyano-5,6-dichloro-1, 4-benzoquinone (D.D.Q.) and this, after extraction, produced a small amount of a green amorphous compound. The ^{1}H nuclear magnetic resonance spectrum again gave very few clues as to the correct structure but mass spectrometry showed peaks at m/e 273 and 244. The molecular weight of the required product is, of course, 273 and the loss of a formyl unit (-29mu) from it would correlate with the fragmentation peak at m/e 244.

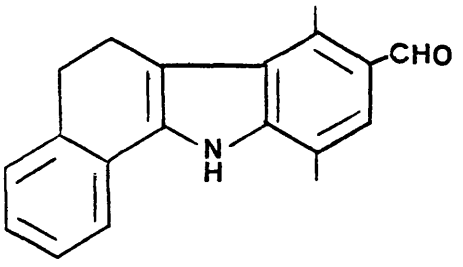
In all the chromatographic work used in this study the products gave rise to an elongated spot rather than a well defined area on the plates. This was worrying but change of solvent system failed to resolve the situation; and we constantly felt that more than one structural isomer was present. Nevertheless, the problem with the ^{1}H nuclear magnetic resonance spectra prevented any solution to this dilemma and rather in desperation we pressed on

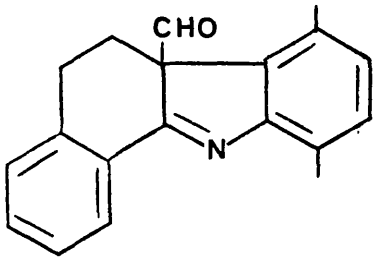
to the last stages of the sequence for the pentacyclic system should be quite stable and should stand up to sublimation conditions which we felt might at least remove any paramagnetic ions.

Using this material the synthesis was carried out and the presumed formyl compound condensed with dimethoxyethylamine to give a white amorphous solid. This gave yet another uninterpretable ^{1}H nuclear magnetic resonance spectrum but spectrometry again gave a peak corresponding to the desired azomethine. Chromatographic purification attempts were unsuccessful although only one spot appeared on thin layer chromatography in many solvent systems. Again we feel that a paramagnetic contaminant was present and so the final stage in the sequence was tried. The azomethine was treated with polyphosphoric acid at $150^{0}C$ for twenty minutes, and the resulting "gum" subjected to chromatography. Instead of showing a streak on thin layer chromatographic plates, this time many individual spots were discernable, and an attempt was made at a separation. One of these spots fluoresced bright yellow under ultraviolet light and using a long slow-running column and eluting with 10% petroleum ether in ethyl acetate this was eluted and gave only a single spot in a variety of solvents. The amount obtained did not allow analysis by ^{1}H nuclear magnetic resonance spectroscopy but the ultraviolet spectrum showed a strong absorbance at λ 298nm and mass spectrometric analysis revealed a molecular ion at m/e296, corresponding to the ring closed product. Further attempts at elucidating the structure and constituents of this mixture were then abandoned. The author speculates that, since the formylation was carried out on a dihydrobenzocarbazole the preferential site of attack may not have been on the C-8 position and that any or all

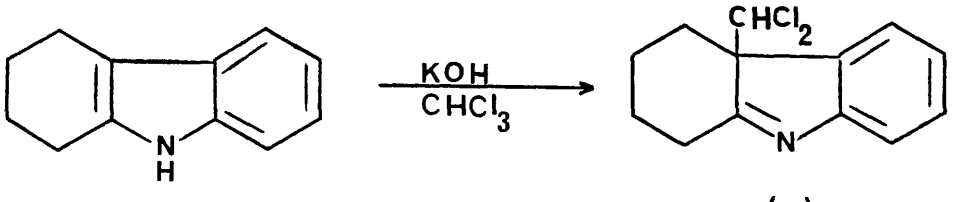
of the compounds, the structures of which are drawn below may have been formed.





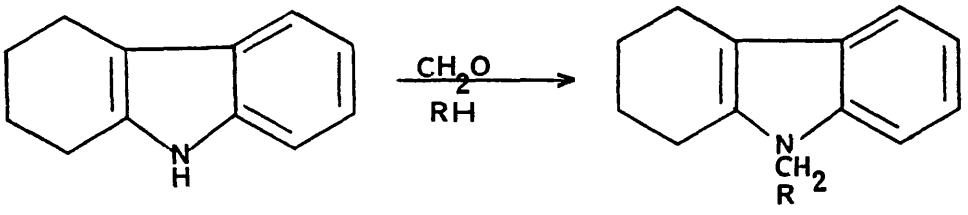


Work carried out by Robinson[78] suggests that the carbazolenine may be a principal product since the reaction between tetrahydrocarbazole and dichlorocarbene afforded 4a-dichloromethyl-1, 2,3,4-tetrahydro[4aH]carbazole (64).



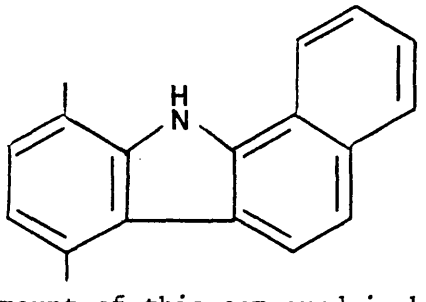
(64)

But alkylation of tetrahydrocarbazole with formaldehyde and an alkane, yields the N-alkylated product.



Since neither of the N-formyl or formylcarbazolenine are likely to yield any ring closed products then it is reasonable to suppose that a small amount of 8-formyl benzocarbazole is present in our mixture. Unfortunately the ultraviolet spectra of model compounds are not available so that some confirmation of these proposals is not possible.

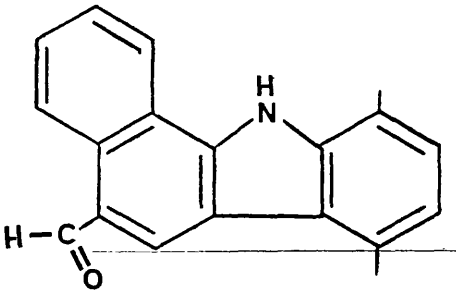
Since it seemed highly unlikely that formylation of the dihydrobenzocarbazole could be effected to give the desired product in acceptable yields; aromatisation was the next obvious course of action. The fully aromatic benzo[a]carbazole was easily prepared by heating in toluene with 10% palladium on charcoal. After purification an analytically pure sample allowed spectroscopic identification as the 7,10-dimethylbenzo[a]carbazole (65).



(65)

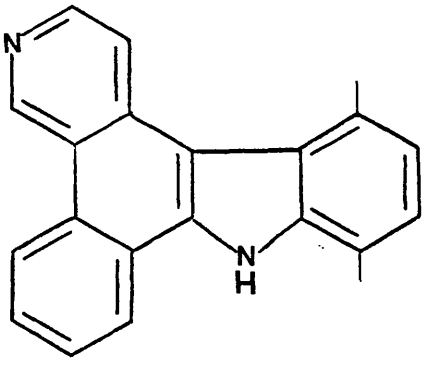
With a large amount of this compound in hand the formylation was carried out, using the same reagents and conditions stated previously. On purification a pale green crystalline product was formed which gave the correct carbon and hydrogen analysis

and a typical vinylogous amide carbonyl absorption at λ 1,650cm^{-1} in the infrared spectrum. The ^{1}H nmr spectrum, however, still showed the AB system of the C-8 and C-9 protons; thus it appeared that formylation had taken place at another site. Decoupling experiments shown overleaf suggest that formylation had taken place at position C-5 (66), which, in retrospect, would be a particularly attractive site since this is the α-position of the naphthalene moiety, and also this site would be made more nucleophilic by the amino group <u>para</u> to this.

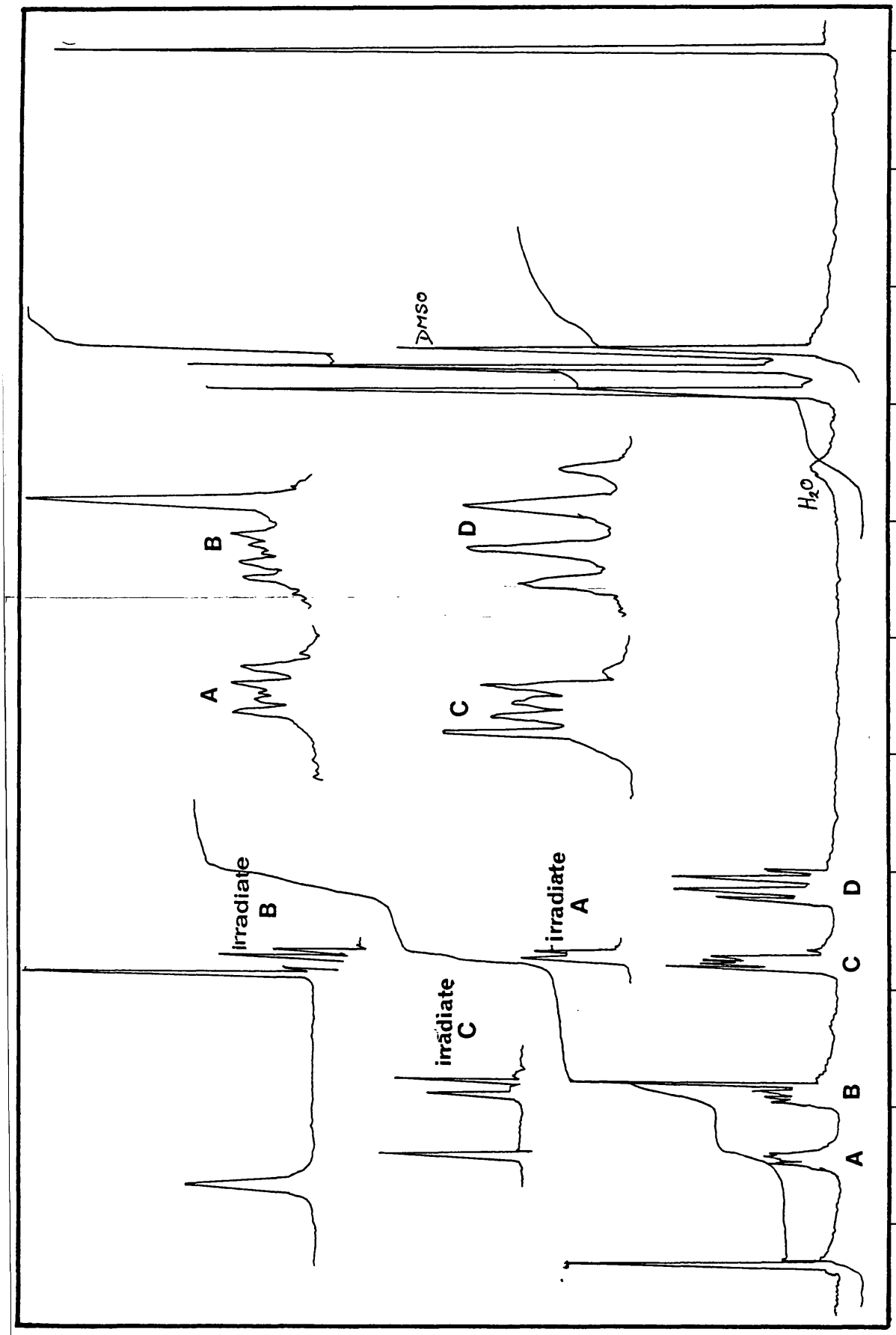


(66)

Although it seemed impossible to prepare benzoellipticine from this method some interest was generated in the possibility of preparing the subsequent pyridobenzocarbazole (67) from the above formyl compound.



(67)


irradiate B
irradiate C
irradiate A
A
B
C
D
DMSO
H_2O
ppm
0
1
2
3
4
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6
7
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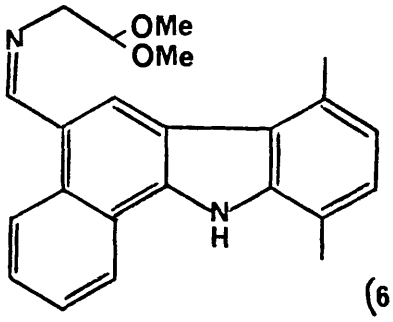
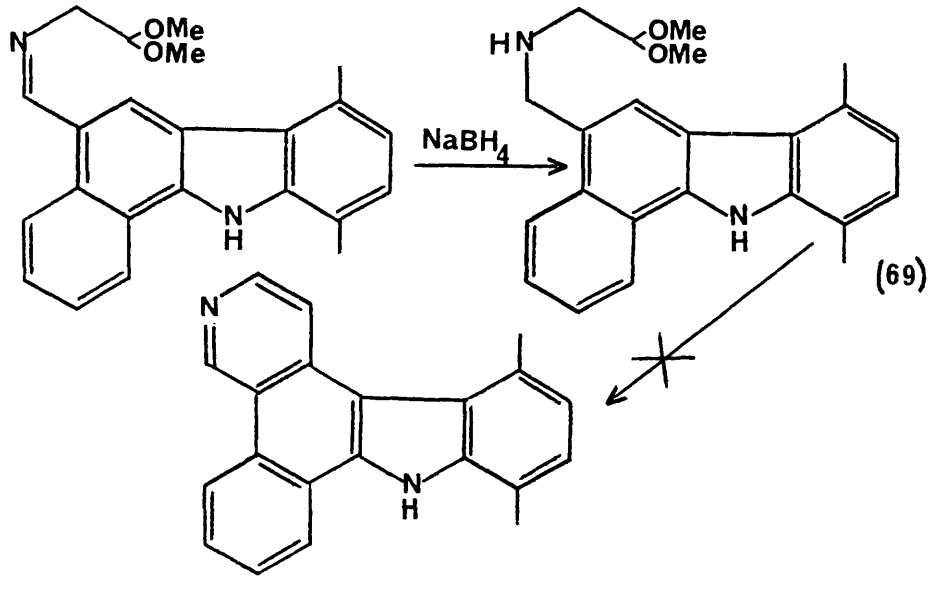
10

The 8-formylbenzo[a]carbazole was easily converted to the azomethine (68) and several attempts at ring-closing this compound were tried.



(68)

Polyphosphoric acid at several different temperatures and reaction times only produced a large quantity of a blue polymeric material, although the ultraviolet spectrum of the crude product showed a strong absorbance at λ 296nm. Chromatography showed this reaction mixture to be a multicomponent system and, as before, a bright yellow fluorescent band was separated but contained only minor amounts of material which exhibited a peak at m/e 296 in the mass spectrum and the ultraviolet spectrum showed maxima at λ 288, 296 and 335nm. These results suggest the possibility of a small amount of the pyridobenzocarbazole being present. The original Cranwell and Saxton ring-closure with hydrogen chloride was attempted on the amine (69) made by sodium borohydride reduction of the azomethine. Here no identifiable products were obtained.



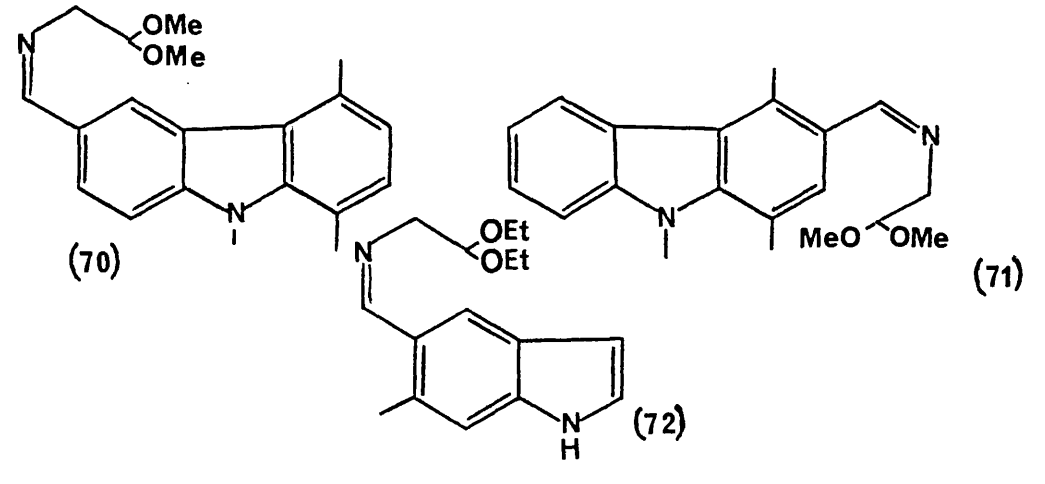
(69)

The next attempt employed Guthrie's[31] method of acid ring closure of the N-tosyl derivative (16). This derivative was prepared by the action of p-toluenesulphonylchloride on the amine in tetrahydrofuran and water containing sodium carbonate. The compound was treated with a variety of acids in tetrahydrofuran and then dioxan, but to no avail. The ultraviolet spectrum remained unchanged after several hours at room temperature. On warming for half an hour with concentrated hydrochloric acid in dioxan the solution turned deep blue and a large amount of high molecular weight compound was formed, no identifiable products were detected.

It is understandable that ring closure to position C-6 is rather difficult since the reactivity of the α position of the naphthalene unit is diminished compared with that of the β and the arc shape of the carbazole structure imposes steric restrictions upon substituents at this position.

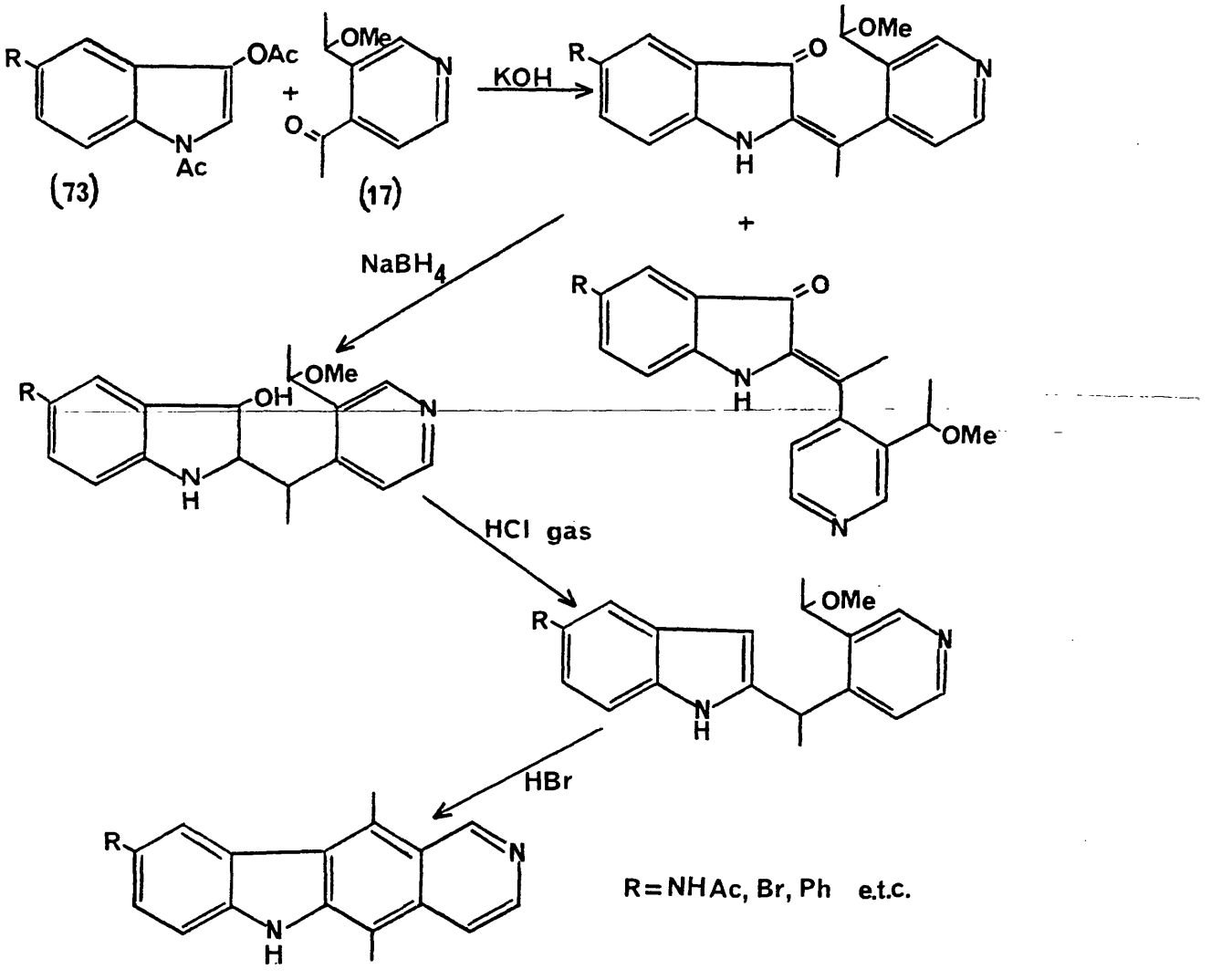
This problem had been faced by Dalton et al[79] who attempted to ring close the azomethine (70), without success. The isomeric azomethine (71) on the other hand ring closed in good yield to the ellipticine.

An interesting model would be the ring closure of the simple indole (72), but this has not been attempted.



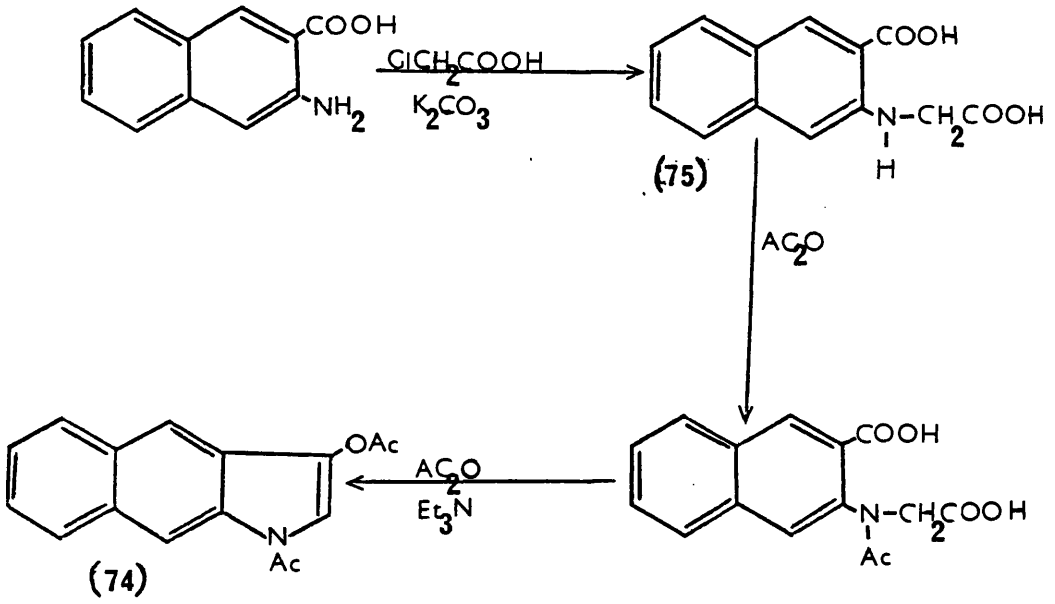
Preparation of Benzoindoxyl

The next reaction sequence used, in attempts towards the preparation of benzoellipticines, was based upon work pioneered by Kilminster and Sainsbury[32] (shown below). This route employed the reaction between a suitably substituted 1,3-diacetylindoxyl (73) and 4-acetyl-3-(1-methoxyethyl) pyridine (17).

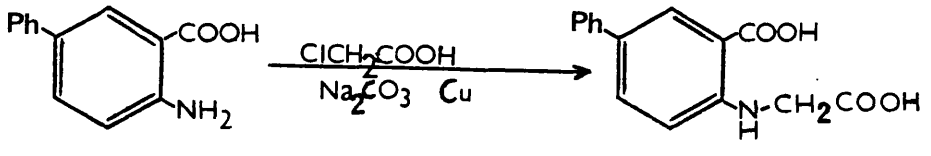


In our case, however, only the 1,3-diacetylbenzo[f]indoxyl (74) is readily available and it was made from 2-amino-3-naphthoic acid with chloroacetic acid and ring-closure of the product with acetic

anhydride, as shown below:

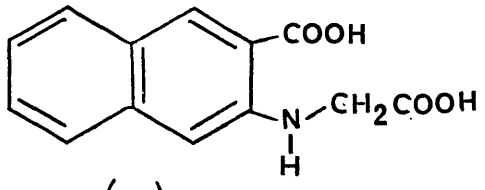


At first it was thought that the condensation between the naphthoic acid and chloroacetic acid might give only low yields of the glycine (75) since the solubility of the potassium salt of 2-amino-3-naphthoic acid was low and large amounts of water needed, but Sainsbury et al[19] had prepared N-(3-carboxybiphenyl-4-yl) glycine (76) using the method of Holt and Petrow[80], which involved the condensation of 5- phenylanthranilic acid with chloroacetic acid in the presence of an aqueous slurry of sodium carbonate and copper powder.



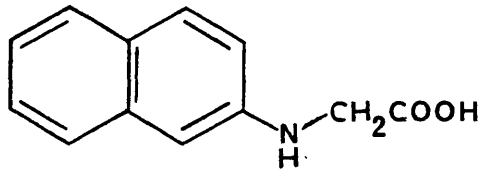
(76)

This technique was applied to the synthesis of (75) although the possibility of decarboxylation of either the naphthoic acid or the glycine-o-carboxylic acid were born in mind since this reaction was carried out at reflux temperatures for several hours.



(75)

This reaction was duly carried out and a slurry of 2-amino-3-naphthoic acid refluxed for 2½ hours in an aqueous solution of sodium carbonate and copper powder. After filtration and acidification a compound was produced which gave only one carboxylic acid carbonyl in the infrared spectrum. Also mass spectrometric analysis revealed a peak at m/e 201; thus decarboxylation had probably taken place allowing the formation of (77)

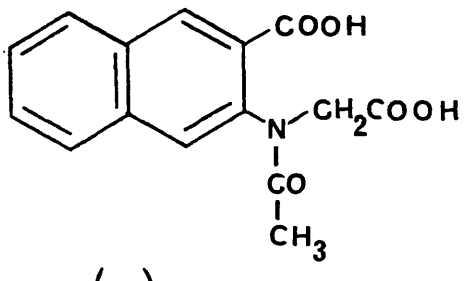


(77)

Preparation of the correct product (75) was eventually achieved using the method[81] of incubating the potassium salts of the anthranilic acid and chloroacetic acid in water at $45^{0}C$ for 24 hours. The resulting solution after filtration and acidification afforded the glycine in 65% yield. As expected, however, large amounts of water were required for dissolution, and thus the isolation of the product proved tedious.

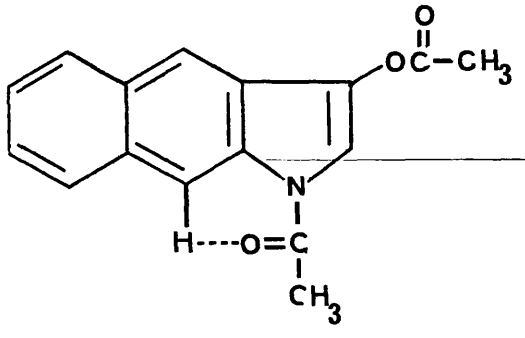
The preparation of 1,3-diacetylbenzo[f]indoxyl from the amino acid was carried out using three different methods to determine the optimum conditions. Firstly the method of Nenitzescu et al[81] was used which involved the N-acetylation of the glycine in an aqueous alkaline solution containing acetic anhydride. Ring closure was achieved by refluxing the N-acetyl compound (78) in acetic anhydride containing a catalytic amount of triethylamine. Again this method had the drawback of large amounts of water being required for dissolution prior to N-acetylation.

The next two methods avoided this by firstly, heating the glycine in acetic anhydride containing sodium acetate and secondly by boiling the glycine in acetic anhydride containing a little triethylamine. Both methods have the added advantage of dispensing with the need to isolate the N-acetyl compound (78).



(78)

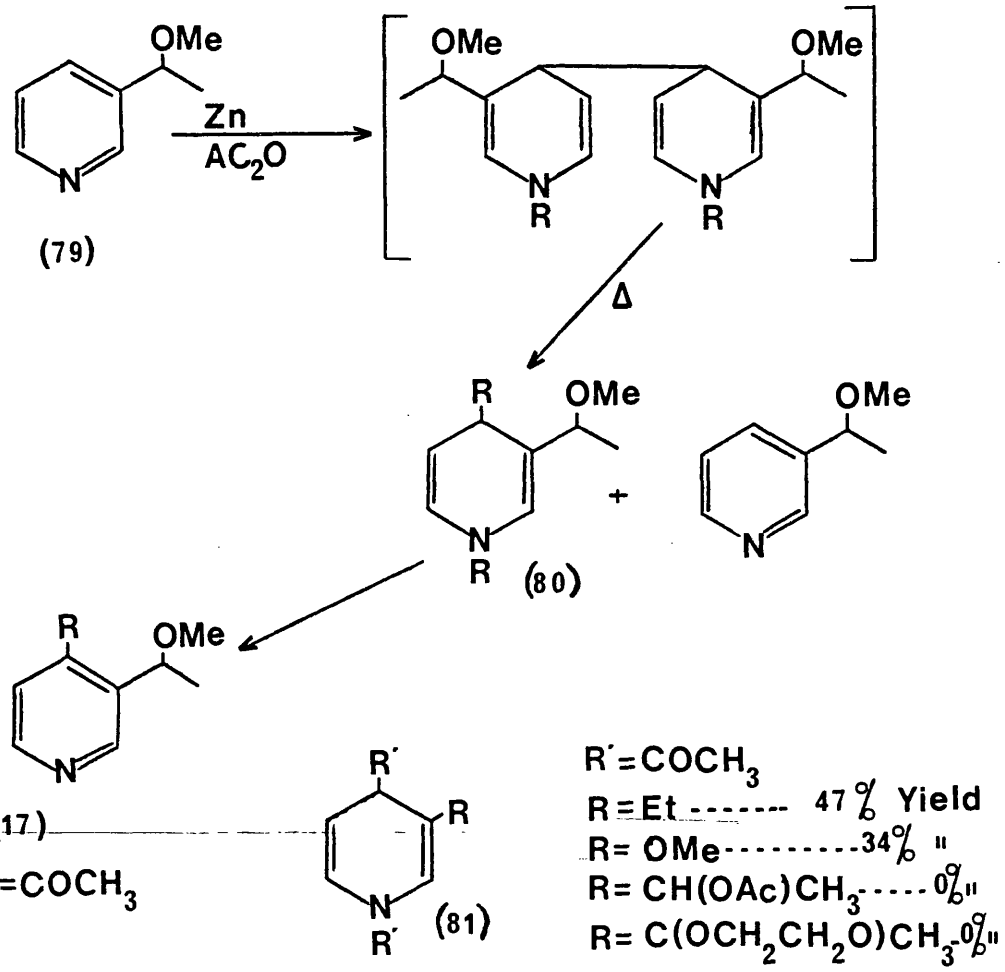
Of the two "non aqueous" methods the latter involving triethylamine was finally chosen since it afforded an easier work up procedure, 1,3-diacetylbenzo[f]indoxyl crystallises as long needles from petroleum ether. In the ^{1}H nuclear magnetic spectrum it shows a one proton singlet resonating at 8.91ppm, which is thought to be due to the C-9 hydrogen atom, its low field position is then associated with the anisotropy of the acetylcarbonyl group attached to the nitrogen atom; the C-4 proton, on the other hand, resonates at 7.91ppm. The other features of the ^{1}H nuclear magnetic resonance spectrum are also compatible with those expected for the required structure.



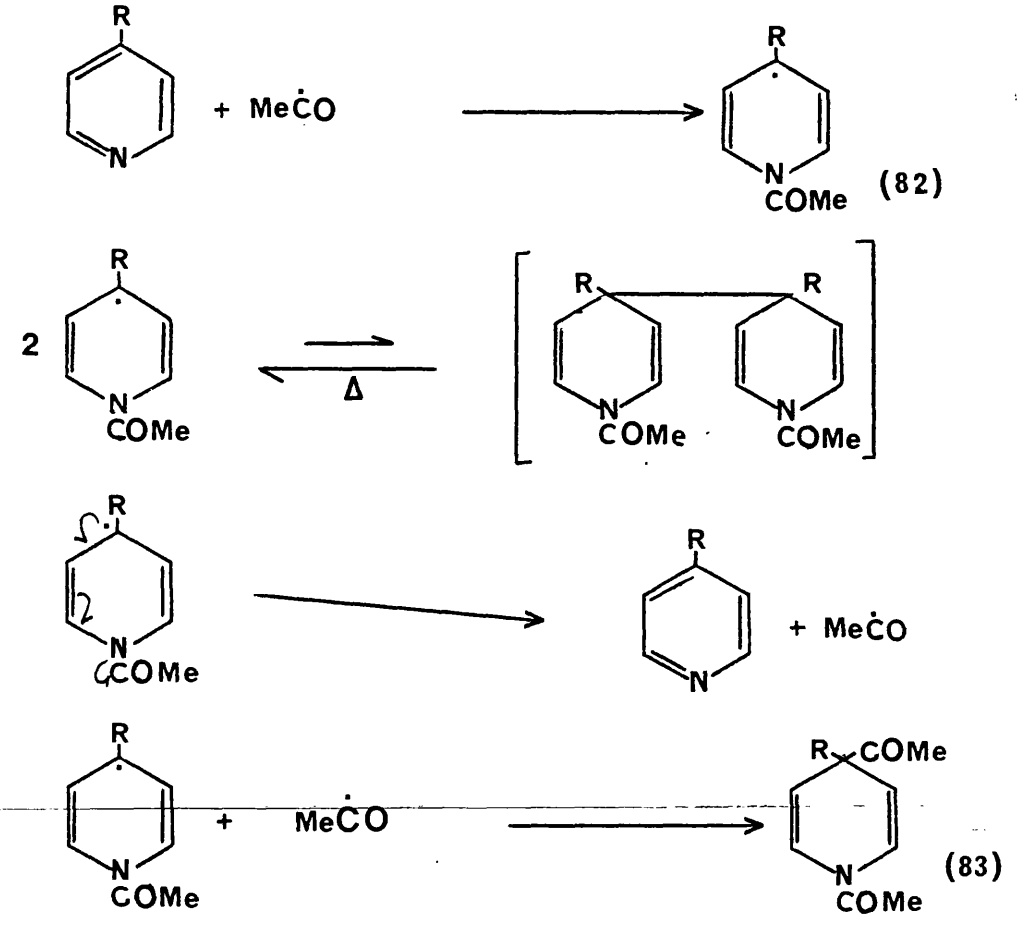
Preparation of 4-acetyl-3-(1-methoxyethyl) pyridine

Previous studies in this laboratory[82] have shown that it is possible to convert 3-(1-methoxy)ethylpyridine (79) into the 1,4-diacetyl-1,4-dihydro derivative (80) by the so called Wibaut-Arens[83] reductive acetylation technique, with acetic anhydride and zinc. This reaction, however, is said to proceed via a dimeric species which then disproportionates into (80) and starting material.

The best yield that can be obtained is therefore only 50% and further constraints are put on the reaction by the size of substituents (81) which often reduce the yield even more.



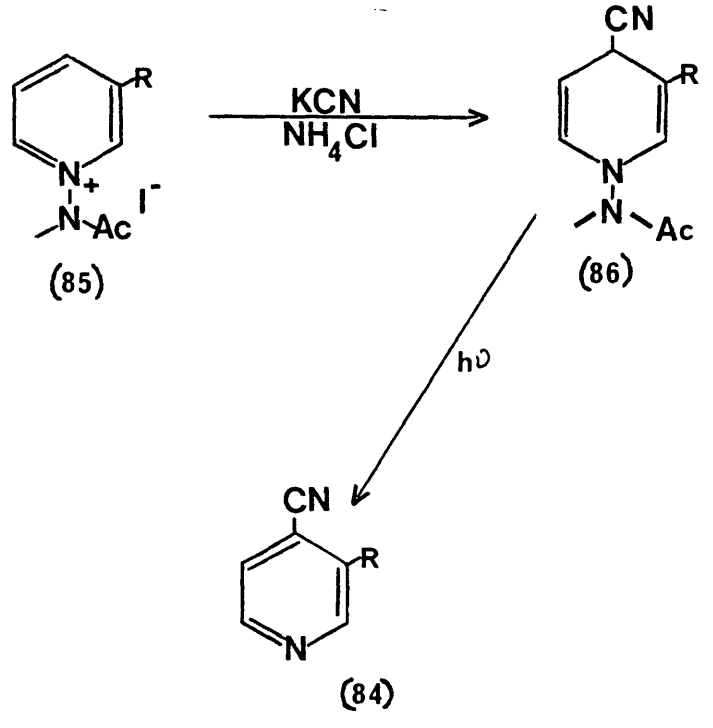
The precise mechanism for these reactions is a little obscure and there is still confusion in the literature despite the large amount of research which has been carried out. One scheme which is particularly attractive although not completely satisfactory involves the dimerisation of the radical (82) which at the temperature of the reaction decomposes back to (82) again. This, then, either reforms the starting pyridine plus acyl radicals, or else, reacts with an acyl radical to form the product (83). These reactions are illustrated in the scheme on the next page. The thermal decomposition of the dimer is now generally believed to involve radicals,[84,85] but there is further disagreement in the literature concerning the nature of the latter stages of the reaction.



The whole procedure can be very frustrating since the initial reductive acetylation step is dependent on temperature and reaction time. When zinc dust is added to a solution of the pyridine derivative (79) maintained at a temperature below $-5^{0}C$ no reaction occured, but when the same reaction was allowed to warm to room temperature an exothermic reaction ensued, causing the formation of a complex reaction mixture. The optimum conditions require a temperature of $-5 - 0^{0}C$ during the four hour addition of zinc then stirring maintained at $0 - 5^{0}C$ for eight hours before allowing the reaction to warm up to room temperature. The product is obtained by heating the 1,4-diacetyl-1,4-dihydropyridine (80) in methanol for several hours. As mentioned previously the yield for this method is low and many reactions are needed to accumulate

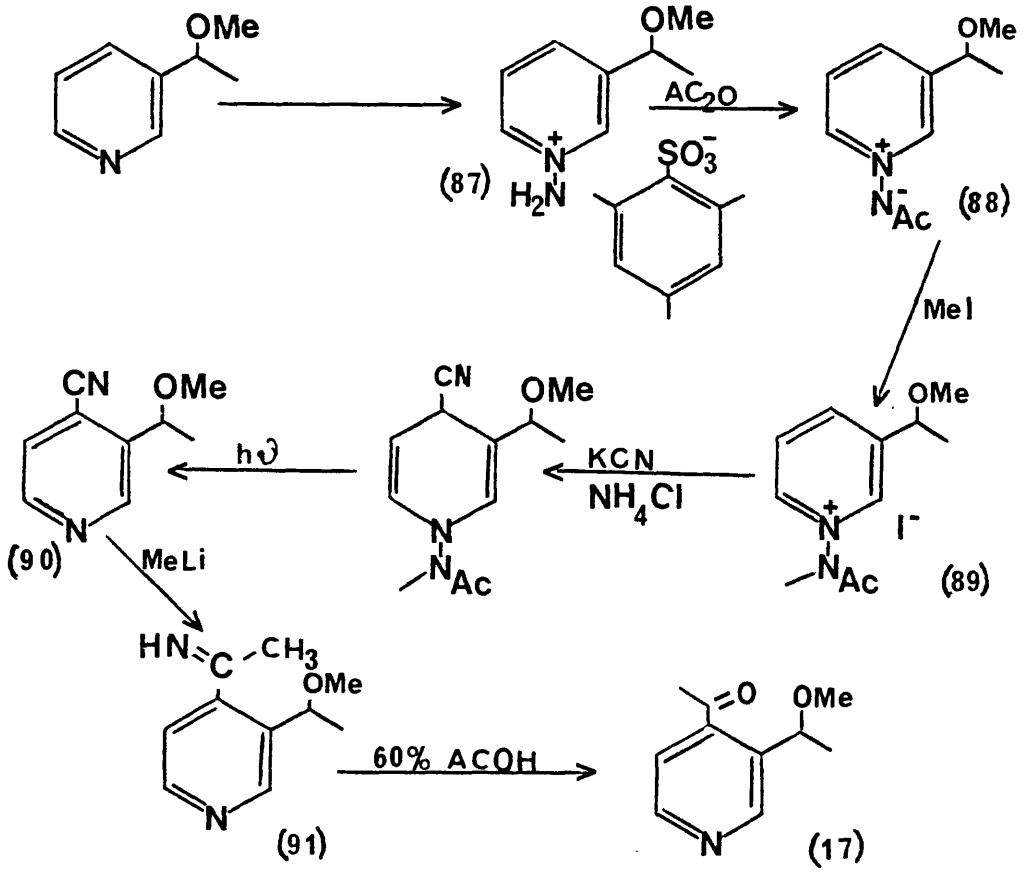
the required amount of pyridine. Also despite the fact that starting material is generated it is not easy to separate this from the dihydropyridine which often oxidizes partially to the corresponding pyridine (17).

A new and more efficient synthesis of 4-acetylpyridines was badly needed and this shortly came about due to work carried out in this laboratory by Sainsbury and Schinazi[37]. Earlier, Suzue et al[86] had shown that 4-cyanopyridines (84) may be prepared by the action of potassium cyanide and ammonium chloride on 1-(N-methylacetamido) pyridinium salts (85). The cyanide ion adding exclusively to the C-4 position of the salt. The 1,4-dihydro derivative (86) which is formed easily aromatises with fragmentation of the N-N bond under the influence of ultraviolet light.

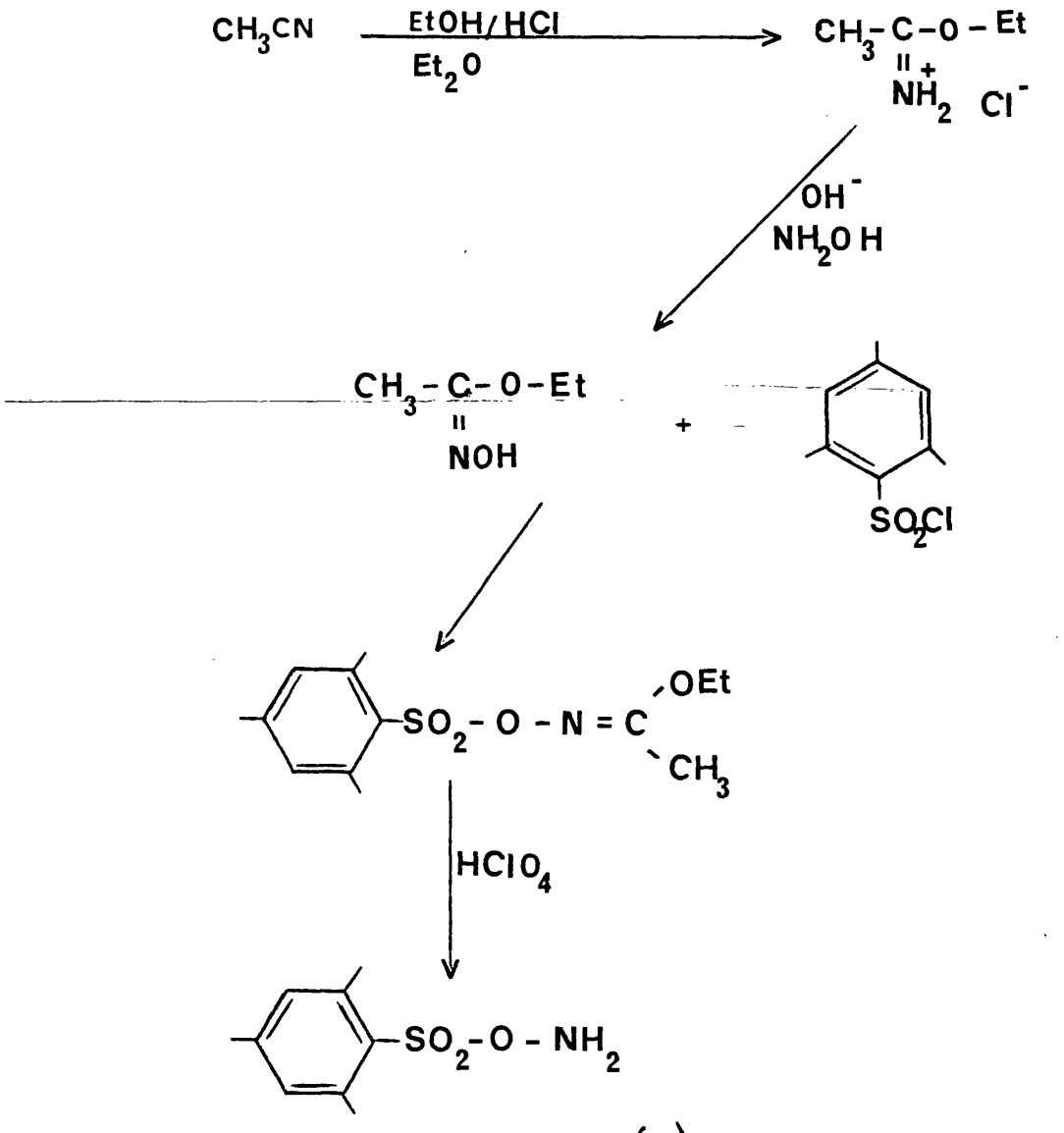


In our case the initial ammination[87] of 3-(1-methoxy) alkylpyridine was accomplished by reaction between the pyridine and o-mesitylene sulphonylhydroxylamine (M.S.H.) to form the ammonated pyridinium salt (87) as a yellow oil.

Treatment of this oil with cold acetic anhydride followed by basification afforded the zwitter ion (88) which, after boiling with methyl iodide, produced the methiodide salt (89). Nucleophilic attack of a cyanide ion in the presence of ammonium chloride gave the dihydrocarbonitrile which aromatised under the influence of ultraviolet light to (90). Treatment of this carbonitrile with excess methyl lithium gave the methylimine (91) as a colourless oil. The imine was easily hydrolysed to the 4-acetylpyridine (17) by stirring in 60% acetic acid; purification being carried out by eluting the 4-acetylpyridine with diethyl ether down a basic alumina column. This scheme is outlined below:-



Mesitylene sulphonyl hydroxylamine (92, M.S.H.) is prepared by a series of reactions shown below. 1-Ethyl-1-oximidoethane was condensed with mesitylene sulphonyl chloride to give ethyl-o-mesitylene-sulphonylacetohydroxamate which was hydrolysed with 70% perchloric acid to give M.S.H.

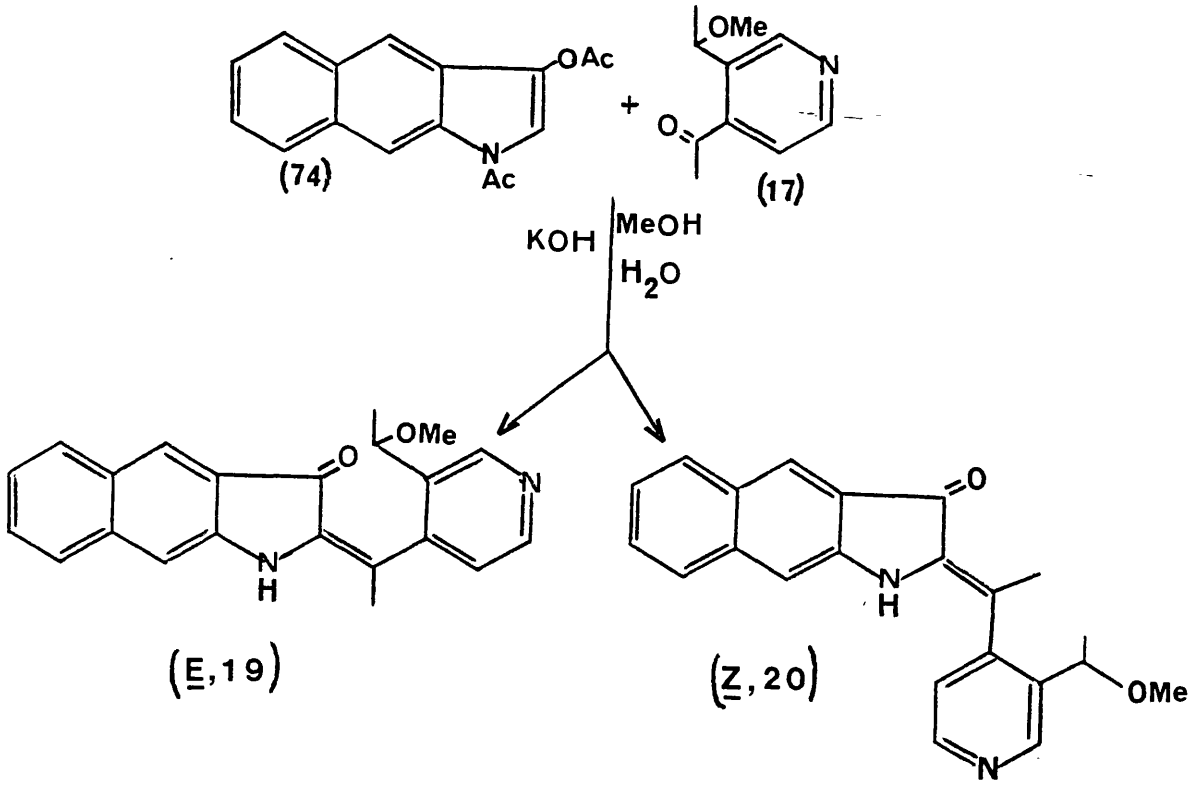


(92)

Benzo-indolinone formation

With both the necessary starting materials in hand an attempt was made to combine the 1,3-diacetylbenzo [f] indoxyl and 4-acetyl-3 [1-(methoxy)ethyl] pyridine. This was carried out by condensing them in aqueous methanol containing potassium hydroxide under a protective atmosphere of nitrogen.

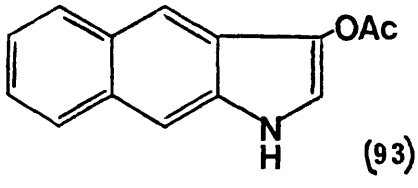
This mixture was set aside for 1 week in the hope that both pairs of diastereoisomeric racemates (E, 19) and (Z, 20) would crystallise. This, however, failed to occur and an extraction procedure was implemented (see page 117).



By pouring the crude reaction mixture into 20% acetic acid a dark blue precipitate was formed. This, after filtration, was extracted with cold and then warm dichloromethane. The cold extraction afforded a dark brown gum but the warm extraction produced a pale pink solid, the 'H' nuclear magnetic resonance spectrum of which indicated that this was the (E)-isomer.

Diastereoisomerism in this isomer (19) causes the methyl group of the pyridyl side chain at C-3 to resonate as a doublet and the methine function of the pyridyl side chain at C-3 to appear as two quartets. The O-methyl group appears as two singlets and similarly the methyl of the pyridyl side chain at C-4 also appears as two singlets.

In order to obtain a little more of the isomers the clear brown acetic acid solution was extracted repeatedly with chloroform which, after drying and evaporation, yielded a mobile brown liquid, presumably concentrated acetic acid. After 24 hours crystals appeared from this liquid, spectroscopic studies of which showed them to be 3-acetylbenzo [f] indoxyl (93). Thus even after one week the condensation between 1,3-diacetylbenzo [f] indoxyl and the pyridine had not been complete and this O-acetylated indoxyl probably formed by the action of acetic acid on benzo [f] indoxyl.

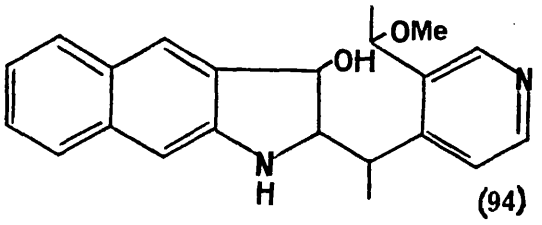


(93)

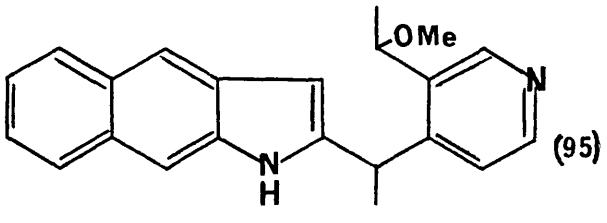
Purification of the mixture of isomers produced by filtration of the acetic acid solution was attempted using 10% petrol in ethyl

acetate on an alumina column. From this column an apparently pure mixture of the isomers was eluted, later more 3-acetylbenzo [f] indoxyl was recovered from this column.

A comparison of the infrared spectra of the pure (E) isomer with the mixture showed two distinct carbonyl bands ν max 1690cm^{-1} for the (E) isomer and νmax 1690 and 1680cm^{-1} for the mixture. This purified mixture of the isomers was subjected to reduction using sodium borohydride in 60% aqueous ethanol and the resulting light red gum, presumably the benzoindolinol (94) treated with hydrogen chloride gas in methanol. From this dehydration reaction another dark brown gum was formed. Attempts at crystallisation from methanol, aqueous ethanol and a variety of other solvents failed. Chromatography indicated the presence of three components, the major of which fluoresced blue and was hoped to be the benzoindole (95).



(94)

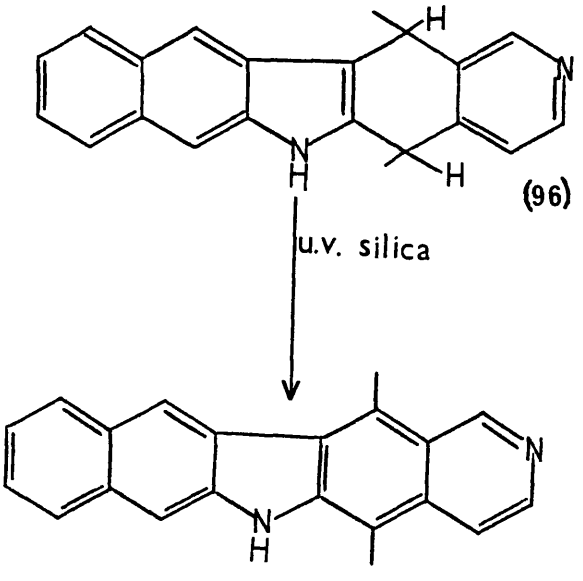


(95)

Purification of this compound also proved difficult and chromatography using a basic alumina column and eluting with chloroform afforded a light brown oil from which a white amorphous solid was produced by boiling with diethyl ether. Infrared and mass spectrometric data indicated that this was the required benzoindole (95) so the final step in the sequence was attemped.

Preparation of 8,9-benzoellipticine

The benzoindole from above was refluxed with 50% hydrobromic acid for about 8 hours and thus obtaining a constant ultraviolet spectrum trace. The acidic solution was allowed to cool to room temperature and then chilled in an ice bath. Filtration of this solution yielded a brown solid which was washed with cold hydrobromic acid. Basifying an aqueous suspension of this solid with ammonia precipitated a light brown solid which was extracted into dichloromethane. The organic phase was dried and evaporated under reduced pressure to yield yet another light brown solid. Since ring closure to ellipticines, using this method, causes the formation of dihydrobenzoellipticine it was necessary to aromatise the supposed dihydrobenzoellipticine (96). This was accomplished by dissolving the light brown solid in methanol, adding a little silica and stirring under ultraviolet light for 30 minutes.



(96)

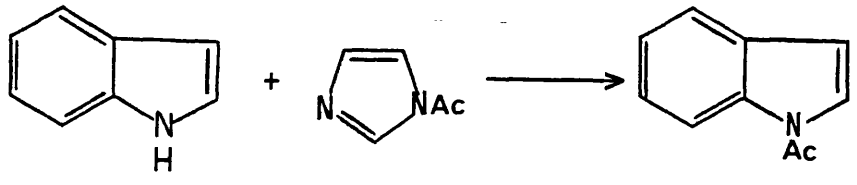
The methanol was then evaporated and the silica washed with dry ether. The product was extracted from the silica by warming with a mixture of methanol and ethyl acetate containing a little ammonia. After drying and evaporation of these solvents the light brown solid residue was sublimed at 250^{0}C under o.1mm Hg for 3 hours. This afforded a small amount of a bright yellow solid which after analysis of spectral data was identified as 8,9-benzoellipticine, which crystallised from ethanol as bright yellow microcrystals. The ultraviolet spectrum of 8,9-benzoellipticine is very similar to ellipticine except, as might be expected, the absorbances are shifted to higher wave lengths due to the increased conjugation.

It is regretted that time did not allow further detailed chromatographic and spectroscopic analysis of the benzoindole (95), and also that the benzoellipticine was not obtained in a great enough quantity to allow biological testing. It is hoped that further work in this field may soon allow the preparation of sufficient quantities of this compound for estimation of its biological activity.

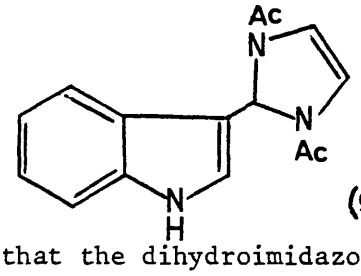
Attempted formylation of 1,4-dimethylcarbazole

During the course of these studies, a publication by Bergmann and Carlsson[88] on a novel formylation of certain molecules using imidazole and trifluoroacetic anhydride was noted. This method allowed the preparation of 3-formylindole, 2,5-diformylpyrrole, 1-formyl-2-methoxy naphthalene and many other formyl compounds in good yield. Since the formylation of carbazoles seems restricted to around the 50% 'mark' it was thought prudent to attempt formylation of 1,4-dimethylcarbazole using the conditions employed by these authors.

The Swedes found that by altering the conditions of a routine preparation of N-acetylindole using N-acetylimidazolethey obtained (97) instead of the expected (98).



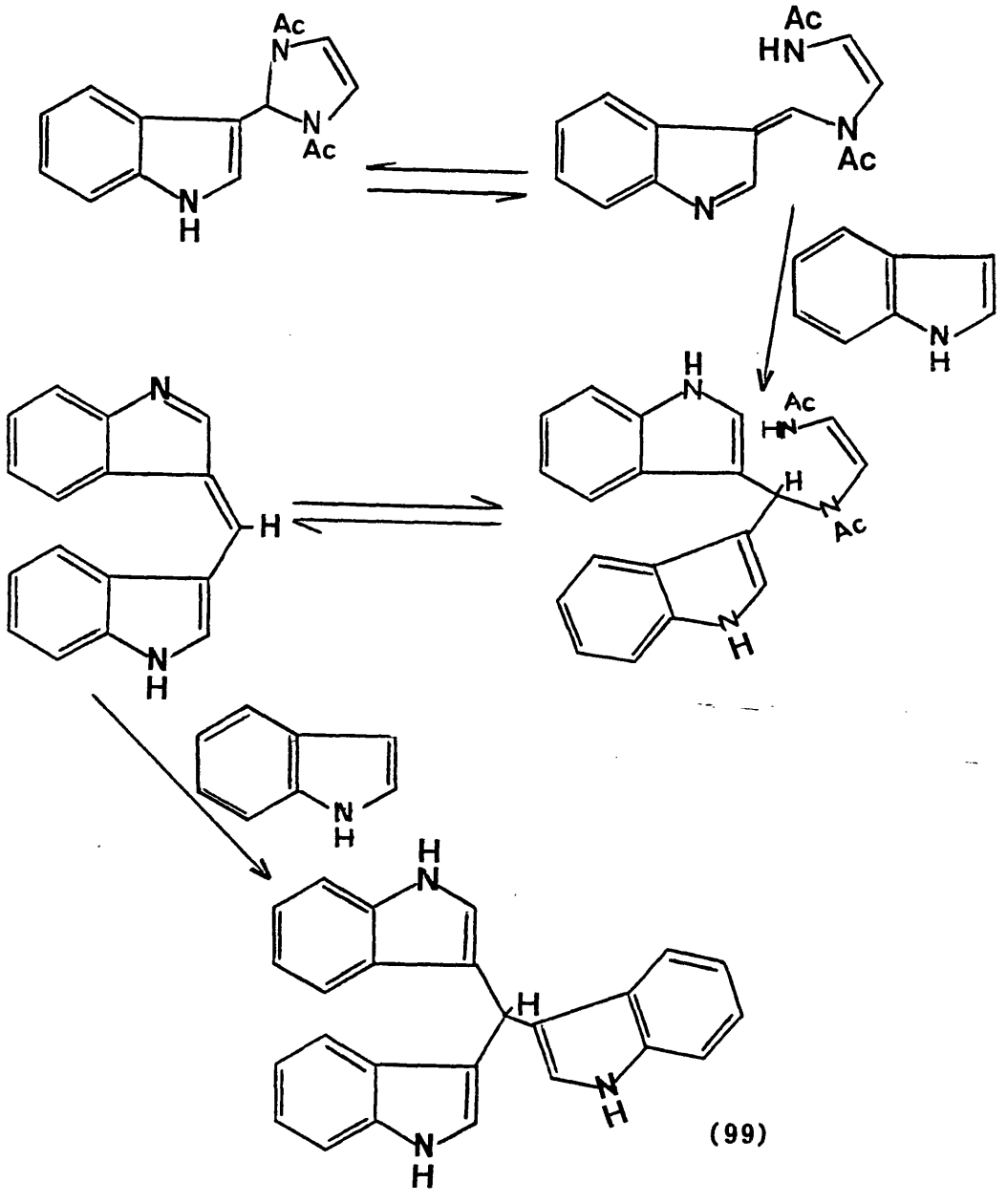
(98)

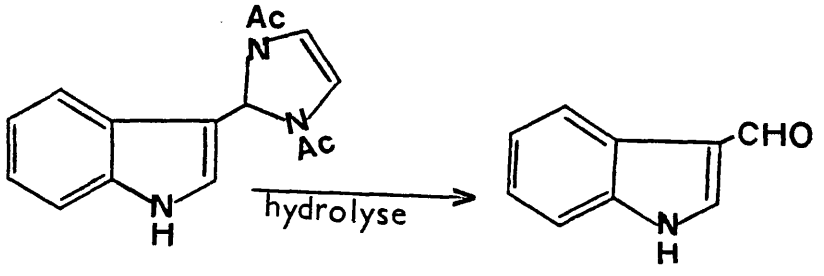


(97)

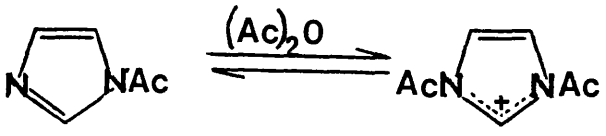
It was recognised that the dihydroimidazole ring is easily ruptured by nucleophilic reagents and by heating this indole in acetic anhydride tris-(3-indolyl) methane (99) was formed, by the mechanism suggested below:

Mild hydrolysis of this compound using sodium hydroxide in aqueous ethanol gave 3-formylindole in good yield.





It appears that because acetic anhydride is present in excess then an equilibrium is set up between N-acetylimidazole and the N,N-diacetylimidazole acetate salt (100).



100

This salt is then able to attack nucleophilic sites on certain activated molecules. By replacing acetic anhydride by trifluoroacetic anhydride the reactivity of the imidazole salt is greatly enhanced. This fluorinated reagent was used in our attempted formylation of 1,4-dimethylcarbazole. The reaction was carried out using molar ratios of carbazole and imidazole and this mixture heated with excess trifluoroacetic anhydride for 1½ hours. The solution was then boiled with 2 Normal sodium hydroxide for a further hour.

The aqueous residue was extracted with chloroform and washed with water and dilute acid. After evaporation of the dried organic phase a white powder had formed. This crystallised as white needles from a methanol/acetone mix. Spectroscopic data, however, indicated that this was not the expected 3-formyl-1, 4-dimethylcarbazole.

All data derived from this compound are given below, and on the basis of this data a tentative structure assigned. (101)

Yield = 1.8g, 49% m.p. 217^{O}C; m/e 715 (M^{+}), 618 (base) 603, 504 and 357.5 (doubly charged ion);

λmax ($\mathcal{E}$) 237 (8,580), 284 (9,653) and 339 (15,730);

ν max (fig. Ia) 3370, 3120, 1710, 1680, 1610, 1230, 1190, 1140, 960, 850, 800 and 740cm^{-1};

δ ($CDCl_3$ & $(CD_3)_2SO$) (fig. I) 2.76 (3H,s), 2.88 (2H, s), 3.06 (3H, s), 7.16 (7H, m), 7.64 (1H, d, J 8Hz), 8.24 (1H, d, J 8Hz) and 11.12 (1H, s br);

(found: C, 47.92; H, 2.78; N, 9.66%).

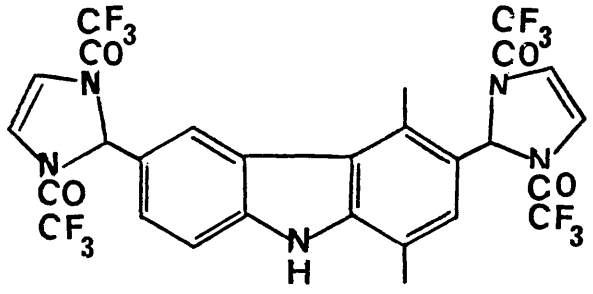
A precision mass measurement carried out by the Physico-chemical Measurements Unit at Harwell, however, gave m/e 291 (M^{+}), 222 (base) and 196; although this could be due to decomposition of the compound since the working temperature of this instrument is higher than our own spectrometer.

The analysis figures show that about 40% of the molecule is composed of fluorine and oxygen and the empirical ratio for carbon, hydrogen and nitrogen is :-

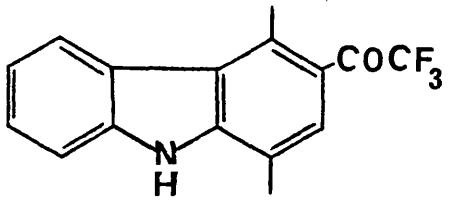
C, 5.78; H, 3.01; N, 1;

m/e 715 indicates the likelihood of an odd number of nitrogens, thus the only molecular formula which gives a correct carbon, hydrogen and nitrogen analysis and a mass of 715 (mu) is $C_{28}H_{17}N_5O_4F_{12}$.

The structure suggested for this molecule (101) seems to fit most of the data and as mentioned previously it is conceivable that the precision mass measurement of m/e 291 is due to decomposition, perhaps to 3-trifluoroacetyl-1,4-dimethylcarbazole (102).



(101)

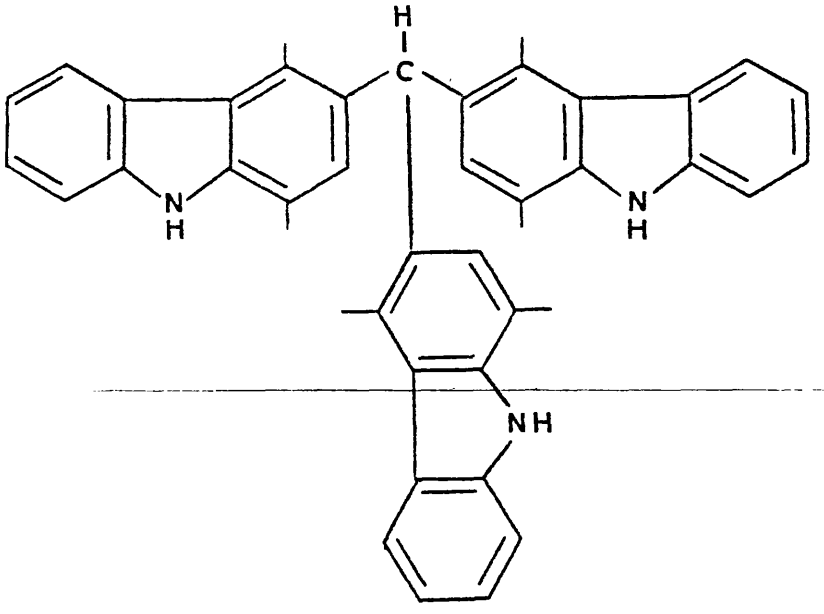


(102)

If this structure (101) is correct then the differences in the amide carbonyl frequences could be due to hydrogen bonding between the carbonyl oxygen atom and the C_4-methyl protons. The two sets of olefinic protons appear to complicate the aromatic region and the two aliphatic imidazole protons seem to resonate at the same position.

Further structural analysis by chemical means was not undertaken due to the limited amount of time. However, the equimolar quantities used for this experiment may have precluded the formation of the apparently desired tris-(1,4-dimethylcarbazyl) methane (103).

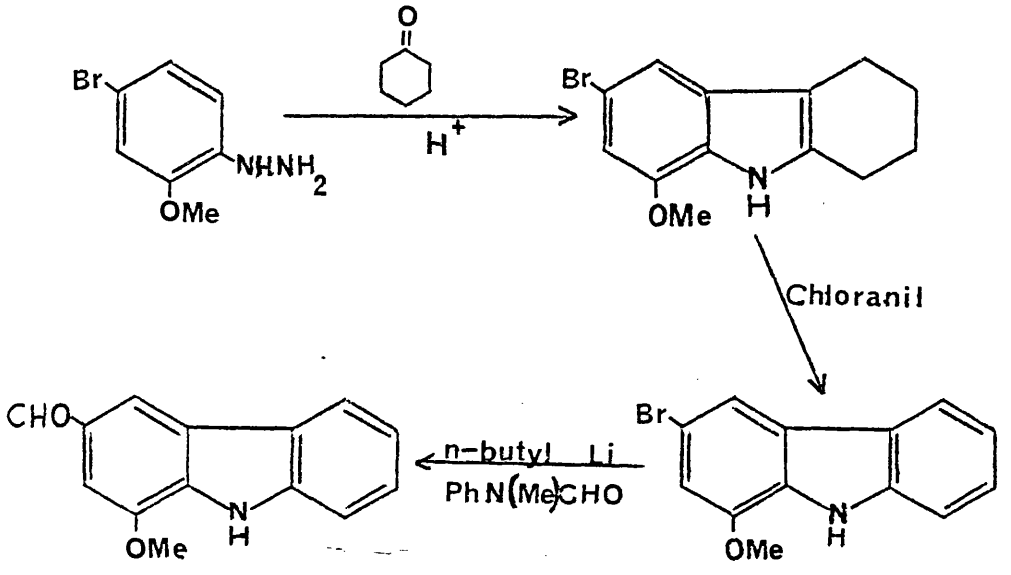
Perhaps the use of 3 mol. of carbazole to 1 mol. of imidazole or by heating the product (101) with excess carbazole in trifluoroacetic anhydride may produce the desired methane derivative.



(103)

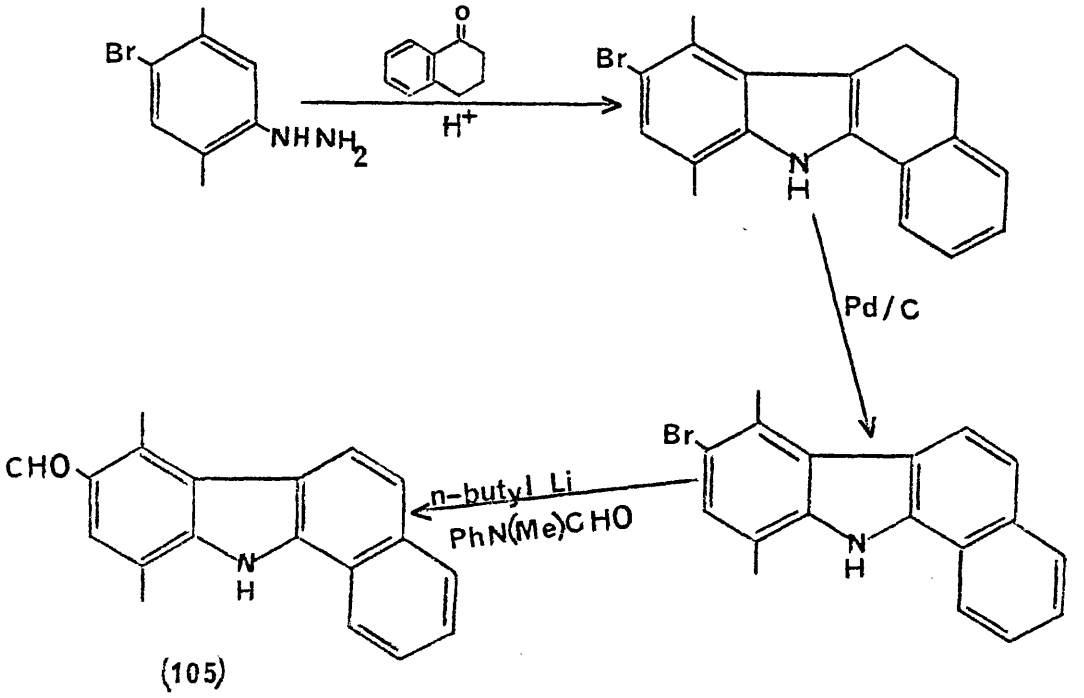
A suggested synthesis of 7,8-benzoellipticine

Work carried out by Crum and Sprague[89] in America on the synthesis of Murrayanine (104), the first carbazole alkaloid, suggested to the author the possibility of preparing 8-formyl-7,10-dimethylbenzo [a] carbazole (105) in a similar fashion. The synthesis of Murrayanine is given below:-



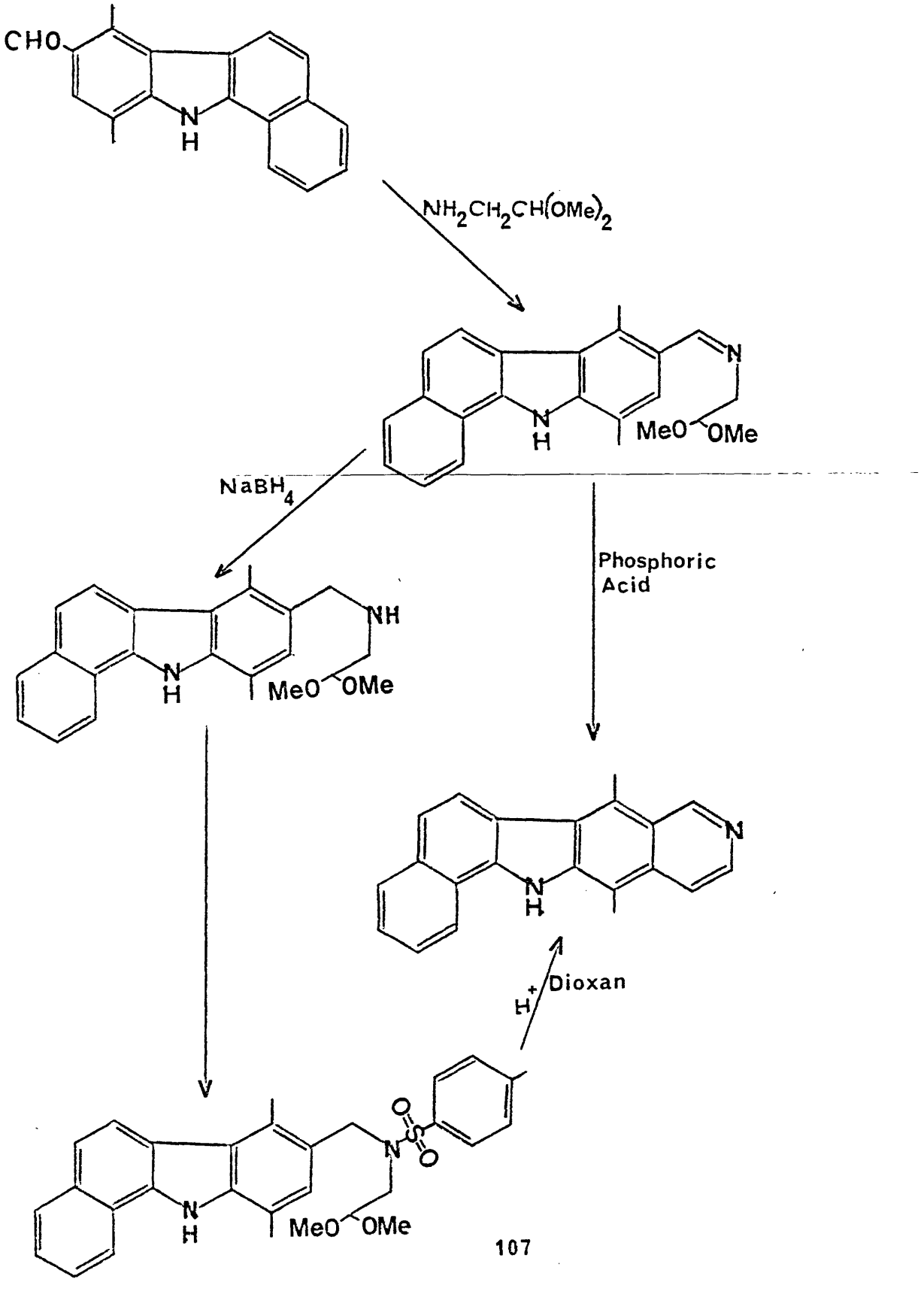
(104)

It is hoped that this procedure could be modified to suit our purposes and a proposed scheme is outlined below:-

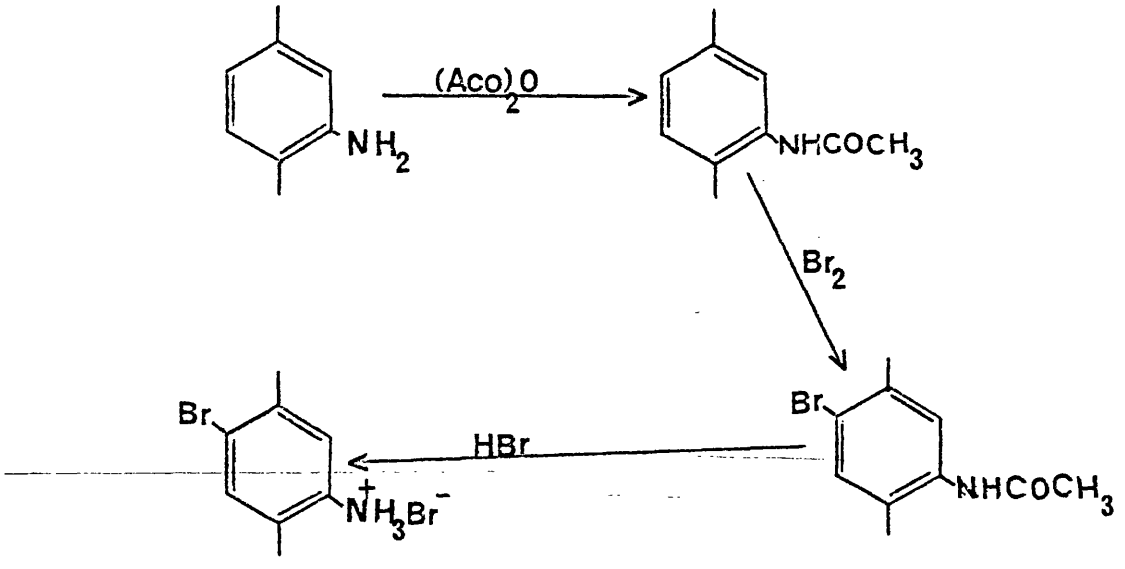


(105)

7,8-benzoellipticine could then be prepared by the standard Cranwell and Saxton method [26,27] of acid ring closure of the azomethine (106) or by Guthrie[31] or Jackson's[90] acid ring closure of the N-tosyl derivative (107).



Time did not allow much progress on this route and our preparative endeavours only proceeded as far as the amine (108). This was easily prepared by the sequence shown below. It was hoped that the required hydrazine could be prepared by diazotisation and then reduction of the diazonium compound using an acidic solution of stannous chloride or sodium bisulphite.



(108)

EXPERIMENTAL

3-[1-(3-Pyridyl)ethyl]indole (25)

Methane sulphonyl chloride ($1cm^3$) in dry benzene was added slowly (4h) to a mixture of indole (1.2g) and the alcohol (28) (1.2g) in the same solvent under reflux in a Dean and Stark apparatus. At the end of the reaction the benzene was decanted from oil which had separated and the latter was then dissolved in water and washed several times with ether. The aqueous phase was basified with ammonia and extracted with chloroform; the combined extracts were dried and evaporated to give an orange coloured oil. Trituration with benzene gave the title compound as a colourless solid. (0.7g, 30%) m.p.173-174^0; m/e 222(M^+), 207 (base), and 144, ν_{max} 3140, 1590 1580 and 1030cm^{-1}; δ ($CDCl_3$; Fig.2) 8.7 br (1H,s,NH), 8.64 (1H,dd, J6 and 2Hz, pyridyl 6-H), 7.6 - 6.9 (7H, M, indole 2-, 4-, 5-, 6-, and 7-, and pyridyl 4-, and 5-H), 4.4 (1H, q, J 10Hz $CH.CH_3$), and 1.7 (3H, d, J 10Hz $CH.CH_3$): (Found: C,81.0; H 6.4; N,12.4. $C_{15}H_{14}N_2$. Requires C, 81.1; H, 6.4: N, 12.6%).

8- Hydroxy-7,8,9,10-tetrahydrobenzo [h] quinoline (33)

A solution of 1-naphthylamine (14.3g) and epichlorohydrin (9.3g) in (chlorobenzene) ($12.5cm^3$) was heated for 8 hours at 136^{0}C in an oil bath. On cooling, crystals separated and the black supernatant liquor was discarded. The purple crystals were washed with toluene ($3x20\ cm^3$) and recrystallised with charcoaling from ethanol to produce a white crystalline mass, of the hydrochloride. This compound was dissolved in water ($50cm^3$) and basified with concentrated ammonia to produce a dense white precipitate which was collected and dried. Crystallisation was carried out from ethanol-water to produce white crystals of the title compound.

(6.7g, 34%) m.p. 150 - 151°, m/e 199 (M^+, base), 180 and 168; ν max 3420 (OH), 3350 (NH), 1540, 1325 and 1100cm^{-1}; λ max (ε) 235 (11,940), 255 (15,522) 340 (3,980)nm; δ ($(CD_3)_2SO$ Fig. 3) 2.62 - 3.74 (5H, m, CH_2-CH-CH_2), 5.08 (1H, d, JOH 2Hz OH) 6.16 (1H, s, N-H). 7.04 (2H, m,5- and 6-H), 7.30 (2H,m, 2-and 3-H), 7.70 (1H, dd, J 7Hz 4-H) and 8.00 (1H, dd, J 8Hz 1-H); (Found C, 78.41; H, 6.58; N, 6.98% $C_{13}H_{13}NO$. Requires C, 78.37; H, 6.57; N, 7.03%).

1H-Benzo [g] indole (29)

8-hydroxy-7,8,9,10-tetrahydrobenzo [h] quinoline (2g) in ethanol (100cm^3) and sodium periodate (2.41g) in water (50cm^3) were added dropwise over 3 hours to an 8% sodium hydroxide solution (100cm^3). The hydroxide solution was kept continuously boiling whilst steam was passed through. The benzoindole was collected from the cooled steam distillate, dried and sublimed to yield the product as shiny white crystals (o.37g, 22%) m.p. 171.5°, m/e 167 (M^+, base) and 139; ν max 3410 (N-H), 815 and 720cm^{-1}; λ max (ε)230 (7,849) and 262 (19,540)nm; δ ($CDCl_3$ Fig. 4) 6.6 (1H, d, J 4Hz 3-H), 7.2 (1H, d, J 4 Hz 2-H), 7.3 - 7.6 (2H, m, 7-and 8-H), 7.46 and 7.7 (2H, dd, J 8 Hz 4-& 5-H), 7.92 (1H, d, J 8 Hz 6-H), 8.2 (1H, d, J 8 Hz 9-H) and 10.44 (1H, s, N-H); (Found C, 86.0; H, 5.40: N, 8.35. $C_{12}H_9N$. Requires C, 86.2; H, 5.38; N, 8.37%).

1H-Benzo [g] indole-2-carboxylic acid

To potassium ethoxide (0.78g K, 0.92g EtOH) in ether, freshly distilled diethyloxalate (2.92g) was gradually added, a clear yellow solution being formed. 2-methyl-1-nitronaphthalene (3.73g)

dissolved in dry ether ($50cm^3$) was then added. The mixture turned from deep red to bright red on standing overnight.

A sodium hydroxide solution (4%, $200cm^3$) was added and the whole solution vigorously shaken and then left for one hour. On acidification two layers formed; a deep red ethereal layer and a white aqueous layer. The ethereal solution was repeatedly extracted with 4% sodium hydroxide and the combined extracts washed with ether, freed from ether and acidified to produce a yellow precipitate of the 1-nitronaphthylpyruvate ester (45%, 2.6g).

An analytically pure sample could not be obtained so the crude pyruvate was carried through to the next reaction.

A gelatinous mass was produced consisting of ammonia ($17cm^3$, $0.88NH_3$) and a hot solution of ferrous sulphate ($22g/24cm^3$ H_2O). The pyruvate ester (2.6g) was dissolved in the gelatinous solution ($35cm^3$) and the mixture refluxed and stirred for one hour. The semi-solid dark mass was then boiled in dilute ammonia and filtered. The filtrate was then acidified with concentrated hydrochloric acid to produce an off-white precipitate of the benzo [g] indole which after crystallisation from acetic acid afforded pure needles of the title compound (1.0g, 52%) m.p. 206 - 207°, m/e 211 (M^+), 167 (base) and 140; λ max ($\mathcal{E}$) 255 (18,360), 285 (19,000) and 304 (6,540); ν max, 3430 (N-H), 3160 - 2570 (COOH), 1650 (C=O), 1570, 845 and 760; δ ($CDCl_3$ & $(CD_3)_2SO$ Fig. 5) 7.16 (1H, s, 3-H), 7.20 - 7.64 (5H, m, 1-, 4-, 7- and 8-H), 7.76 (1H, d, J 8 Hz 6-H), also 8.64 (1H, d, J 8 Hz 9-H) and 12.20 (1H, s br COOH); (Found: C, 73.89, H, 4.28; N, 6.64; $C_{13}H_9NO_2$ Requires C, 73.93; H, 4.26; N 6.63%).

1H-Benzo [g] indole

1H-Benzo [g] indole-2-carboxylic acid (2g) was heated to 215^{0} for 2 hours in quinoline (10cm^{3}) containing copper powder (0.5g). After the reaction had cooled it was poured into water and repeatedly extracted with ether. The ether layer was washed with 2N hydrochloric acid, 2N sodium bicarbonate and then water. After drying the ether was removed to yield a light brown solid which after sublimation afforded 1H-benzo [g] indole (0.98g, 62%) m.p. 172 (Lit,[39] 172); identical in all spectroscopic properties to 1H-benzo [g] indole produced by the preliminary experiment.

6,7-Benzoxindole (35)

Chloroacetyl chloride (8cm^{3}) was slowly added, with stirring, to a solution of 1-naphthylamine (14.3g) in sodium dried benzene (200cm^{3}). After addition a dense white solid precipitated, this mixture was stirred for 1½ hours and then a further aliquot of benzene (100cm^{3}) was slowly added to the benzene solution and the whole reaction shaken. The organic phase was separated, dried and evaporated under reduced pressure to yield chloroacetyl-1-naphthylamine (20.8g, 95%), m.p. 138 - 139^{0}; ν max 3260 (N-H), 1670 (C=O), 1550 (C=O), 800 and 770cm^{-1}; δ ($CDCl_3$ & $(CD_3)_2SO$), 4.32 (2H, s, $-C\underline{H}_2$), 7.2 - 8.0 (8H, m, 2-, 3-, 4-, 5-, 6-, 7-, 8- and N-H).

The compound prepared above (20g) was treated with aluminium chloride (10g) in nitrobenzene (100cm^{3}) at 180 - 185^{0}C for ¾ hour. The solution was allowed to cool and poured onto ice. The solid that formed was filtered and dried to yield 6,7-benzoxindole as a white solid (12.5g, 75%). m.p. 145 - 146^{0}C; νmax 3245 (N-H), 1665 (C=O), 1570, 1510, 820 and 765cm^{-1}; δ ($CDCl_3$), 4.2 (2H, s, $C\underline{H}_2$), 7.2 - 8.0 (6H, m, 4-, 5-, 6-, 7-, 8-, and 9-H) and 8.7 (1H, s, N-H).

Attempted reduction of 6,7-benzoxindole

6,7-benzoxindole (2g) in tetrahydrofuran ($20cm^3$) was added slowly to a refluxing slurry of lithium aluminium hydride (0.3g) also in tetrahydrofuran. Once addition was complete (½ hour) the solution was refluxed for a further ½ hour and the excess lithium aluminium hydride destroyed by the addition of ethyl acetate. Once the solvents had been removed the 'gummy' residue was partitioned between ether and water. The ether layer was then dried and removed to yield a dark brown oil. νmax 3220, 3250 and $1680cm^{-1}$. m/e 183 (M^+).

This oil was dissolved in ether ($30cm^3$) and the ether washed with 2N hydrochloric acid (3 x $15cm^3$). On basification with sodium bicarbonate and re-extraction (ether $20cm^3$) another brown oil was afforded. νmax 3360, 2980, 2870, 1580, 1460, 790 and $770cm^{-1}$; m/e 169 (M^+).

Further purification by chromatography or distillation failed to improve the purity of this compound.

1,3-Diacetylindoxyl

(i) Phenylglycine-o-carboxylic acid

A slurry of anthranilic acid (25g) in water ($20cm^3$) was dissolved in water (15g) containing sodium hydroxide (8g). Separately, to a solution of chloroacetic acid (17.4g) in water ($25cm^3$) was added anhydrous sodium carbonate (10g).

Both solutions were heated to 40^0 to aid dissolution and then mixed thoroughly and left for 24 hours at 40^0. The solid mass which was formed was filtered and dissolved in water ($200cm^3$) containing sodium hydroxide (8g) and acidified with concentrated hydrochloric acid.

Phenylglycine-o-carboxylic acid was collected as a light tan coloured precipitate (29.8g, 84%) m.p. 217 - 218^0 (Lit. [58] 218 - 219^0)

(ii) N-Acetylphenylglycine-o-carboxylic acid

To a solution of anhydrous sodium carbonate (8.3g) in water (83cm^3) was added phenylglycine-o-carboxylic acid (9.5g) in small portions. After the acid had dissolved, acetic anhydride (7.3cm^3) was added slowly and the mixture stirred for 30 minutes. Acidification with concentrated hydrochloric acid gave colourless needles of the acetyl derivative (10.1g, 89%) m.p.208^0 (Lit.[58]208^0)

(iii) Ring closure to N,O-diacetylindoxyl

N-Acetylphenylglycine-o-carboxylic acid (5g) was heated under reflux with acetic anhydride (25cm^3) and triethylamine (5cm^3) under nitrogen for 20 minutes. The acetic anhydride was evaporated in vacuo and the oily residue extracted several times with hot petroleum (60 - 80^0). The petrol extracts were combined, heated under reflux with charcoal, filtered, reduced in volume and allowed to cool. N,O-diacetylindoxyl crystallised as long colourless needles. (3g, 65.5%) m.p. 80 - 81^0 ν max 1740 (NHCO) and 1700 ($OCOCH_3$)cm^{-1}. δ ($CDCl_3$). 2.30 (3H, s, $C\underline{H}_3CO$-OR), 2.50 (3H, s, $C\underline{H}_3CON$),

7.05 - 7.50 (3H, m, 5- 6- and 7-H),

7.64 (1H, s, 2-H) and 8.4 (1H, m, 4-H).

N- Acetylindoxyl

N,O-diacetylindoxyl (2.5g) was added to a solution of sodium sulphite .7H_2O (7g) in water (50cm^3) at 70 - 75^0. Stirring and heating was maintained until hydrolysis was complete. The light brown solid which had formed was removed by filtration, washed with water and dried in a dessicator.

N-Acetylindoxyl (1.7g 85%) crystallised as light tan coloured needles from isopropanol.

m.p.135^0. ν max 1725 (NHCO) and 1675 (C=O)cm^{-1}, δ ($CDCl_3$): 2.3 (3H, s, $COC\underline{H}_3$), 4.25 (2H, s, $COC\underline{H}_2N$), 7.0 - 7.8 (3H, m, 5- 6- and 7-$\underline{H}$), 8.4 (1H, m, 4-$\underline{H}$).

Reduction of N-acetylindoxyl

N-Acetylindoxyl (1g) was dissolved in ethanol (75cm^3) and the solution cooled to 5^{0}C. Sodium borohydride was added portion-wise to this mixture which was stirred and kept at 5^{0}C for 30 minutes. The solvent was removed in vacuo and the residue partitioned between chloroform and water. The chloroform layer was washed with water, dried and evaporated to yield a light brown solid which was washed with a little ethanol and filtered to yield 3-hydroxyindoline (0.56, 73%). m.p. 93^{0}C (Lit.[91] 96^0) ν max 3490, 3280, 1615, 1495, 1210, 1075, 930 and 770cm^{-1}; λ max (ε) 242 (7000) and 297 (2150)nm.

Dehydration of 3-hydroxyindoline (49)

The indoline (250mg) was dissolved in dry ether (10cm^3) and dry hydrogen chloride gas passed through for ½ hour with stirring. On removal of the solvent a dark brown glass was left which, on sublimation, produced a small amount of glistening white crystals of indole (65mg. 30%) m.p. 51^0 (Lit.[92] 52^0). Spectroscopic data of this compound were identical to an authentic sample of indole.

Attempted preparation of 2-ethyl-6,7-benzoindole

To a slurry of 2-methyl-1-nitronaphthalene (18.7g) in concentrated hydrochloric acid (185cm^3), iron powder (50g) was slowly added and the mixture allowed to react. After the reaction had subsided it was refluxed for ½ hour and then allowed to cool. The cooled solution

was filtered and the filtrate washed with 2N hydrochloric acid. The clear colourless solution was then caustiously basified, with cooling, using 30% sodium hydroxide and the resultant precipitate extracted with ether. The organic phase was dried and evaporated under reduced pressure to yield an off white powder which crystallised from petrol to yield 1-amino-2-methylnaphthalene (12.7g 81%) m.p. 33^{0} (Lit.[93] 32^{0}).

1-amino-2-methylnaphthalene (10g) was refluxed with proprionic anhydride ($15cm^{3}$) for $\frac{3}{4}$ hour and to the resulting cooled solution water was added until crystallisation affected. The white crystalline solid was filtered and dried to yield (51) 2-methyl-1-proprionamidonaphthalene (12.9g, 95%) m.p. 147 - 148^{0}; ν max 3260 (N-H), 1660 (C=O), 1580, 1500, 805 and 740cm^{-1}; δ ($CDCl_3$) 2.25 (3H, s, Ar-C<u>H</u>$_3$), 2.45 (3H, t, CH_2-C<u>H</u>$_3$), 3.50 (2H, q, CH_3-C<u>H</u>$_2$), 7.23 (1H, s, N-<u>H</u>) and 7.30 - 7.85 (6H, m, 3-, 4-, 5-, 6-, 7- and 8-<u>H</u>).

An intimate mixture of the above compound (8g) and sodium amide (3g) was heated in an oil bath for 20 minutes at 25^{0}C. After this mixture had cooled to room temperature, water ($20cm^{3}$) was slowly added and the residue extracted with ether. The ether layer was dried and evaporated under reduced pressure to yield a dark green gum which became resinous on attempted distillation.

<u>Xylyl hydrazine</u>

With vigorous stirring 1-amino-2,5-dimethylbenzene (215g) was added to a solution of concentrated hydrochloric acid ($445cm^{3}$) in water ($200cm^{3}$). This mixture was chilled to -5^{0}C, stirring was maintained whilst a solution of sodium nitrite (131g) in water ($200cm^{3}$) was added dropwise.

The clear orange diazonium solution was maintained at $0^{0}C$ and stirred while a solution of stannous chloride dihydrate (900g) in hydrochloric acid ($600cm^3$) and water ($600cm^3$) was added over a 4 hour period. The yellowish slurry was stirred as it was permitted to warm to room temperature; and stirring continued for a further 24 hours. The pale yellow tin complex which formed was collected, dried and washed with ether ($200cm^3$). This complex (600g) was stirred into water ($1300cm^3$) and the slurry stirred vigorously while it was being treated with a solution of sodium hydroxide (450g in $600cm^3$ H_2O), the temperature being kept below $15^{0}C$. The crude hydrazine was extracted with ether (3 x $150cm^3$) and the ether solution was washed with water and dried ($MgSO_4$). This dry solution was then diluted with a further quantity of dry ether ($300cm^3$) and this bulk solution split into two equal parts. Dry hydrogen chloride gas was passed through each and the pure hydrochloride filtered and dried in a dessicator (220.7g, 72%), m.p. $206^{0}C$ (Lit.[94] $206^{0}C$), free base m.p. $74^{0}C$ (Lit.[94] $74^{0}C$).

5,6-Dihydro-7,10-dimethyl-11H-benzo[a]carbazole (59)

Xylyl hydrazyl hydrochloride (35.2g) was added to a solution of 20% hydrochloric acid ($500cm^3$) and refluxed until clear. 1-tetralone (29.2g) was added to the refluxing solution over a period of 4 hours. On cooling a light brown solid precipitated out. The liquor was poured off and the solid broken up in 95% ethanol and filtered to produce a white powder. Crystallisation from 95% ethanol afforded white plates (37.3g, 76%), m.p. 165 - 166^{0}, m/e 247 (M^+ base), 232 and 217; ν max (Fig.6) 3430 (NH), 1610, 810 and 730 - $750cm^{-1}$; λ max (ε) 255 (24,450) and 347 (6,175)nm; δ($CDCl_3$, page 56) 2.45 (3H, s, 10-CH_3), 2.70 (3H, s, 7-CH_3), 3.0 - 3.30 (4H, m,

J 15.5Hz, CH_2-CH_2), 6.80 (2H, dd, J 10Hz, 8- and 9-H), 7.25 (4H, m, 1-2-3- and 4-H) and 8.0 (1H, bs, N-H) (Found C, 87.43; H, 6.83; N, 5.72. $C_{18}H_{16}N$ Requires C, 87.38 H, 6.92; N, 5.66%).

Formylation of 5,6-dihydro-7,10-dimethyl-11H-benzo [a] carbazole

The title benzocarbazole (26g) was heated on a steam bath with a mixture of phosphoryl chloride (20.95g) and N-methylformanilide (19.3g) in o-dichlorobenzene (70cm^3) for 3½ hours. After completion of the reaction sodium acetate (10g) was added to the dark oily slurry which was then steam distilled for approximately 5 hours to remove the solvent. The dark green solid residue which remained was dried by pressing into a filter paper and then grinding up with anhydrous magnesium sulphate and charcoal. Extraction of this mixture was carried out using a soxhlet extractor and toluene as the solvent. After 3 hours the yellow toluene extract was boiled with charcoal, filtered hot, evaporated to low bulk and allowed to cool. Yellow micro crystals which became powdery on agitation, precipitated from this solution.
(12.4g, 43%) m.p. 198 - 204°C; λ max (ε) 260 (18,150), 290 (7,920), 300 (8,250), 342 (10,450) and 390 (9,280)nm; ν max 3500 br, 1710, 1670, 1620, 1610, 1260, 860, 800 and 770cm^{-1}; m/e 275 (M^+), 273 (base) and 244; (Found: C, 83.41; H, 6.22; N, 5.21; $C_{19}H_{17}NO$ Requires C, 82.91; H, 6.18; N, 5.09%).

Attempted aromatisation of formyl-7,10-dimethylbenzo [a] carbazole:

A mixture of the above formyl compound (2g) and D.D.Q. (2g) in toluene (20cm^3) was refluxed for 5 hours. Once the reaction had cooled it was warmed and stirred with 2N sodium hydroxide (5cm^3) and the toluene layer then separated, dried and evaporated to yield a dark brown solid.

Crystallisation of this solid could not be effected using any of the solvents tried. Purification was partially achieved using chloroform petrol and a silica column. This produced a light green solid which still gave a very broad melting point, (0.740g,37%) m.p. 205 - 212^{0}C; ν max 3410, 1710, 1650, 1260, 1120, 850, 805 and 790cm^{-1}. m/e 273, (M^{+}) and 244 (base).

Attempted Preparation of 7,8-Benzoellipticine

The above formyl compound (500mg) was heated with excess dimethyoxyethylamine (300mg) on a steam bath for 3 hours. The resulting orange solution was then refluxed with benzene (10cm^{3}) using a Dean and Stark apparatus to remove any water present. After removal of the solvent the resulting orange oil would not crystallise, but precipitation was achieved bypouring an ethereal solution of this oil into petrol. The off white solid so produced could not be crystallised from any solvent used and chromatography failed to improve the purity.

The yield from this reaction was (600mg, 87%), m/e 360 (M^{+}) and 329 (base); λ max 263, 291, 335 and 361nm, ν max 3350, 1610, 1155, 860 and 800cm^{-1}.

The suspected azomethine (500mg) from the above reaction was heated with polyphosphoric acid at 150^{0}C for 20 minutes. Water was added to the resulting dark brown solution and this mixture then poured into 2N sodium hydroxide. This solution was then extracted with ethyl acetate which on evaporation gave a dark brown 'gum'. Chromatographic separation of a single yellow fluorescent band (R_f 0.6, silica T.L.C. 10% petrol/ethyl acetate) was carried out using 20% petrol in ethyl acetate on a silica column. This band

gave a single spot in various mixtures of chloroform and petrol. On evaporation of the chromatography solvents a minute amount of a yellow solid (~1mg) was produced. m/e 296 (M^+, base), 281 and 266; λ max 266, 296 and 313 nm.

7,10-Dimethyl-11H-benzo [a] carbazole. (65)

The dihydrobenzo [a] carbazole was refluxed in xylene ($100cm^3$) containing a little 10% Pd/C for one and a half hours. On cooling a white crystalline mass appeared. This was collected, washed with ether and crystallised from ethanol to afford the title compound (36.4g, 98.4%), m.p. 161 - 162°C, m/e 245 (M^+, base), 230 and 215; ν max 3440 (NH), 1515, 810 - 840 and 740cm^{-1}; λ max (ε) 255 (23,275), 283 (25,480), and 303 (12,740) nm; δ ($CDCl_3$), 2.55 (3H, s, 10-CH_3), 2.83 (3H, s, 7-CH_3), 6.98 (2H, dd, J, 7Hz 8- and 9- H), 7.50 (4H, m, 1-, 2-, 3-, & 4-, H) (Found C, 88.27; H, 6.11; N, 5.74. $C_{16}H_{15}N$ requires C, 88.13; H, 6.16; N 5.71%). Also 8·00(2H, m,5- and 6-H) 8·54(1H, bs, N-H). Fig.7

5-Formyl-7,10-dimethyl-11H-benzo [a] carbazole (66)

The benzo [a] carbazole (65, 29.4g, 0.12 mol.) was treated with a mixture of N-methylformanilide (0.17 mol.) and phosphoryl chloride (0.17 mol.) in o-dichlorobenzene ($60cm^3$) and heated on a steam bath for 3½ hours. On completion of the reaction the black oily residue was transferred to a flask containing sodium acetate (46.0g) in water ($200cm^3$) and the whole solution steam distilled for approximately 4 hours. The dark grey solid which had formed was then dried by pressing into a filter paper at the pump and then ground up with charcoal and magnesium sulphate. This mixture was then extracted using a soxhlet extractor for approximately 10 hours using toluene ($300cm^3$) as the solvent. This solution was then charcoaled and on

cooling, deposited light green crystals of the title compound, (14.8g, 45%) m.p. 286 - 287°, m/e 273 (M^+, base) and 244; ν_{max} 3260 (N-H), 2725 (aldehyde, C-H), 820 and 730 - 760cm^{-1}; λ_{max} (ε) 250 (21,840), 290 (30,849) and 260 (6,279)nm; δ ($(CD_3)_2SO$ Fig. 8) 2.70 (3H, s, 10-C<u>H</u>$_3$), 2.90 (3H, s, 7-C<u>H</u>$_3$), 7.1 (2H, dd, <u>J</u>, 8 Hz, 8- and 9-<u>H</u>), 7.70 (2H, m, 2- and 3-<u>H</u>), 8.80 (1H, s, 6-<u>H</u>), 8.90 (1H, m, 1-<u>H</u>), 9.50 (1H, m, 4-<u>H</u>), 10.32 (1H, s, <u>H</u>-C=O), and 12.12 (1H, bs, N-<u>H</u>); (Found C, 83.56; H, 5.55; N, 5.10; $C_{19}H_{15}NO$. Requires C, 83.49; H, 5.53; N, 5.12%).

<u>5-(2,2-Dimethoxyethyliminomethyl)-7,10-dimethyl-11H-benzo [a] carbazole</u> (68)

5-formyl-7,10-dimethyl-11H-benzo [a] carbazole (5.46g, 0.002 mol.) was dissolved in excess dimethoxyethylamine (4.20g, 0.04 mol.) and heated on a steam bath for 3 hours. Dry benzene (20m^3) was added to the resulting orange solution and this was refluxed for 1½ hours in a Dean and Stark apparatus to remove any water present. After evaporation of the solvent it was found that the orange oil would not crystallise, but on pouring an ethereal solution (7cm^3) into petroleum ether (40 - 60°, 20cm^3) a fine off-white precipitate was produced. This was collected and crystallised twice from benzene to afford white crystals of the title compound (6.55g, 91%) m.p. 132 - 134°; m/e 360 (M^+), 329 299, 285 (base) 270 and 258; λ_{max} (ε) 280 (30,960), 295 (27,000) and 348 (18,720) nm, ν_{max} 3330(N-H), 1620, 800, and 740cm^{-1}; δ ($CDCl_3$ Fig. 9), 2.56 (3H, s, 10-C<u>H</u>$_3$), 2.76 (3H, s, 7-C<u>H</u>$_3$), 3.55 (6H, s, 2 x OC<u>H</u>$_3$),

3.90 (2H, d, J 6Hz $C\underline{H}_2$-CH), 4.82 (1H, t, J 6Hz $C\underline{H}$-CH_2), 7.04 (2H, dd, J 8Hz 8- and 9-H), 7.56 (2H, dd, J 4Hz 2- and 3-H), 8.16 (1H, dd, J 4Hz 1-H), 8.50 (1H, s, 6-H), 8.90 (1H, s, CH=N), 9.17 (1H, dd, J 4Hz 4-H) and 10.87 (1H, s, N-H):

(Found C, 76.82; H, 6.82; N, 7.91. $C_{23}H_{24}N_2O_2$ Requires C, 76.64; H, 6.71; N, 7.77%).

5-(2,2-Dimethoxyethylaminomethyl)-7,10-dimethyl-11H-benzo [a]carbazole (69)

The azomethine (68,6g.) was dissolved in a mixture of ethanol ($35cm^3$) and tetrahydrofuran ($10cm^3$). To this solution excess sodium borohydride was added until effervescence ceased, the reaction being monitored by u.v. spectroscopy. Stirring was maintained for ½ hour. On completion of the reaction water ($15cm^3$) was added and the organic solvents removed, under vacuum. The white slurry that remained was extracted with chloroform and after removal of the solvent yielded an off-white powder which was purified by crystallisation from petroleum ether (80 - 100^0), (5.73g, 95%) m.p. 117 - 119^0; m/e 362 (M^+) and 258 (base); ν max 3440(N-H), 3230 (N-H), 810 and $750cm^{-1}$; δ ($CDCl_3$), 2.45 (3H, s, 10-$C\underline{H}_3$), 2.70 (3H, s, 7-$C\underline{H}_3$), 2.90 (2H, d, J 6Hz $C\underline{H}_2$-CH), 2.91 (1H, s, $N\underline{H}$-CH_2), 3.33 (6H, s, 2 x $OC\underline{H}_3$), 3.53 (1H, t, J 6Hz $C\underline{H}$-CH_2), 5.21 (2H, s, $C\underline{H}_2NH$), 7.00 (2H, dd, J 8Hz 8- and 9-H), 7.52 (2H, dd, J 4Hz 2- and 3-H), 8.10 - 8.35 (3H, m, 1- 4- and 6-H) and 9.30 (1H, s, N-H).

5- N-p-toluenesulphonyl-(2,2-dimethylethylamino)-methyl -7,10-dimethyl-11H-benzo [a] carbazole

A mixture of the amine (69, 5g), sodium carbonate (1.5g),

tetrahydrofuran ($100cm^3$) and water ($50cm^3$) was stirred with p-toluenesulphonyl chloride (2.62g) at room temperature for 3 hours. Water was then added and the precipitated product filtered and crystallised from ethyl acetate, to give pure crystals of the title compound (5g, 70%) m.p. 165 - 167°, m/e 516 (M^+) and 259 (base) ν max 3350(N-H), 1380 1150, 880 and 750cm^{-1}; λ max (ε) 215 (16,000), 247 (26,316), 256 (24,252), 283 (28,900) and 304 (7,224); δ ($CDCl_3$/$(CD_3)_2SO$ Fig. 10), 2.46 (3H, s, 10-CH_3), 2.68 (3H, s, 7-CH_3), 2.82 (3H, s, CH_3-Ar-S), 2.96 (6H, s, 2xOCH_3), 4.96 (2H, s, CH_2-N), 7.10 (2H, dd, J 8Hz 8- and 9-H), 7.35 and 7.84 (4H, dd, J 8Hz CH_3-Ar-SO_2), 7.56 (2H, m, 2- and 3-H), 8.12 (1H, s, 6-H), 8.44 (2H, m, 1- and 4-H) and 9.93 (1H, s, N-H). 3·22 (2H, d, J 6Hz, CH_2-CH-), 4·10 (1H, t, J 6Hz, -CH-CH_2).

Attempted ring closure of 5-(2,2-dimethoxyethylimino methyl)-7,10-dimethyl-11H-benzo[a]carbazole (68)

The imine (1g) was dissolved in warm ortho-phosphoric acid (45g) and the deep red solution heated to 140 - 145° over a period of 5 minutes and then kept at this temperature for a further 20 minutes. The cooled reaction mixture was then washed into 2N sodium hydroxide ($300cm^3$) to produce a dark blue precipitate. This was extracted with chloroform (3 x $200cm^3$) dried, and the solvent removed to low volume. T.L.C. showed this to be a multicomponent system but using neutral alumina, eluting with 20% petrol-ethyl acetate one yellow fluorescent spot was apparent. This spot eluted from a neutral alumina column employing 10% petrol-ethyl acetate. On evaporation of the solvent this yellow compound showed only one component under different T.L.C. conditions and gave m/e 296 and λ max 296nm.

The imine was also treated with polyphosphoric ester at 125^{o}C for 20 minutes. Column chromatography again gave a yellow fluorescent spot which was eluted using the same conditions as stated above. Once again only a very small amount was produced which gave the same m/e and λ max as above.

Attempted ring closure of 5-(2,2-dimethoxyethylamino methyl)-7,10-dimethyl-11H-benzo[a]carbazole (69)

The amine (1.5g) was dissolved in absolute ethanol (250cm^3) and this solution was saturated with dry hydrogen chloride gas and then boiled for 1½ hours. After which the solvent was removed and the residue partitioned between chloroform (40cm^3) and water(30cm^3). After drying and removal of the chloroform the residue was subjected to chromatography using many different solvents and solvent mixtures. No identifiable products, however, could be eluted from any of the columns attempted.

Attempted ring closure of 5- N-p-toluenesulphonyl-(2,2-dimethoxyethylamino)-methyl -7,10-dimethyl-11H-benzo [a] carbazole

The tosyl compound (1g) was dissolved in dioxan (40cm^3) and 6N hydrochloric acid (20cm^3) and stirred at room temperature overnight. The following morning a blue precipitate had been produced; this was removed by filtration, washed with dioxan and then suspended in water (200cm^3). Basification with dilute ammonia appeared to leave the blue suspension unchanged. Extraction of this solution with ethyl acetate produced a blue solution which, after drying and evaporation of the solvent, yielded a blue solid which defied any chromatographic analysis using a variety of chromatography columns and solvents.

1,3-Diacetyl benzo [f] indoxyl

(i) Naphthylglycine-o-carboxylic acid

To a slurry of 2-amino-3-naphthoic acid (20g) in water ($50cm^3$) was added a solution of potassium hydroxide (6.0g) in water ($100cm^3$). This mixture was warmed and stirred until dissolution occured.

Separately, chloroacetic acid (10.2g) in water ($150cm^3$) was neutralised with potassium carbonate (14.9g).

Both these solutions were warmed to 45^0C, mixed, and left at this temperature for 24 hours. The resulting dark brown solution was filtered whilst warm and acidified with concentrated hydrochloric acid to yield a yellow precipitate of naphthylglycine -o-carboxylic acid which was filtered, and the remaining solution extracted with chloroform to yield more of the desired acid.

(17.0g, 65%) m.p. 214 - 215^0, ν max 3360 (NH), 3300 - 2600 (acid OH's), 1710 (sat. C=O), 1690 (aryl C=O), 1580, 1510, 860 and $740cm^{-1}$.

(ii) N-acetyl naphthylglycine-o-carboxylic acid

To a solution of anhydrous potassium carbonate (10.2g) in water ($135cm^3$) was added the acid (12g) in small portions. After dissolution, acetic anhydride (10g) was slowly added and the mixture stirred for 30 minutes. Acidification with concentrated hydrochloric acid gave pale yellow needles of the acetyl derivative; extraction of the solution, after filtration, also produced some of the N-acetyl product.

(10.1g, 72%), m.p. 203 - 204^0C.

(iii) Ring closure to 1,3-diacetyl benzo [f] indoxyl

The N-acetyl naphthylglycine-o-carboxylic acid (90g) was boiled with acetic anhydride ($35cm^3$) and triethylamine ($8cm^3$) under nitrogen for 20 minutes. The acetic anhydride was evaporated under reduced pressure to yield a dark brown gum which was exhaustively extracted with petroleum ether (60 - 80^0C), the extracts were combined, heated with charcoal, filtered, reduced to low bulk and allowed to cool 1,3-diacetyl benzo [f] indoxyl crystallised as long pale yellow needles (5.1g, 61%), m.p. 146 - 147^0 λ max ($\mathcal{E}$). 243 (18,000), 270 (26,200), 333 (4,810) and 350 (6,141)nm; ν max 1750 (ester), 1680 (amide), 820, 840, 760 and $740cm^{-1}$; δ ($CDCl_3$ Fig. 11) 2.37 (3H, s, $C\underline{H}_3CO$-O), 2.54 (3H, s, $C\underline{H}_3$-CON), 7.44 (2H, m, 5- and 8-H), 7.77 (1H, s, 2-H), 7.90 (3H, m, 4- and 7-H) and 8.90 (1H, s, 9-H); m/e 267 (M^+), 225 and 183 (base); (Found C, 71.65; H, 4.78; N,, 5.33; $C_{16}H_{18}NO_3$. Requires C, 71.82 H, 4.90; N, 5.26%).

(iv) Ring closure to 1,3-diacetyl benzo [f] indoxyl

Naphthylglycine-o-carboxylic acid (5g) was added, with stirring, to a mixture of acetic anhydride ($15cm^3$) and triethylamine ($6cm^3$) and the resulting solution stirred at room temperature for 15 minutes. The solution was then refluxed under nitrogen for a further 20 minutes, after which time the acetic anhydride was removed under reduced pressure and the resulting brown slurry repeatedly extracted with petroleum ether (60 - 80^0). On cooling this afforded crystals of the title compound (4.3g, 78%) identical in all spectroscopic properties to the indoxyl prepared by the previous method above.

3-(1-hydroxyethyl) pyridine (28)

To 3-acetylpyridine (100g) dissolved in ethanol (500cm^3) sodium borohydride was added in small portions over a period of 30 minutes. The temperature was maintained at less than 30^0 by means of an ice bath during addition. Completion of the reduction was judged by obtaining a constant ultraviolet spectrum. Distilled water was then added and the ethanol removed by evaporation under reduced pressure. The yellow slurry was diluted with distilled water and extracted with chloroform (3x200cm^3), the organic extracts were combined and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a yellow oil which was distilled under 0.3mm pressure at 90^0 to give (96.6g, 95%) of a colourless oil. m/e 123 (M^+), 108 (base), 80 and 59.26 metastable for 108 - 80; λ max (ε) 263 (6,500), 256 (5,830) and 268 (4,690)nm. ν max 3,500 - 3,100 (OH), 2,950 and 2,900 (CH_3), 1610, 1600 and 1410cm^{-1}; δ ($CDCl_3$) 1.5 (3H, d, C$\underline{H}_3$), 4.9 (1H, q, C$\underline{H}$), 7.2 (1H, m, 5$\underline{H}$), 1.7 (1H, m, 4-$\underline{H}$), 8.25 (1H, m, 6-$\underline{H}$), 8.4 (1H, s, 2-$\underline{H}$), and 8.55 (1H, sbr, OH).

3-(1-chloroethyl)-pyridine

The hydroxy compound (20g) was dissolved in dry benzene (50cm^3) and thionyl chloride (20cm^3) added dropwise while the temperature was maintained between 5 - 10^0. After addition the reaction was stirred for ½ hour and allowed to warm up to room temperature. Evaporation of the solvent yielded a brown gum which was dissolved in cold water (50cm^3) and washed with ether (15cm^3). The aqueous phase was then basified, with cooling, using solid sodium bicarbonate and the

resultant slurry extracted with ether (2x50cm^3), the ether layers were combined and washed with brine, dried and the solvent removed to yield a yellow mobile oil. (21.6g, 94%), ν max, 650cm^{-1}.

3-(1-methoxyethyl)-pyridine (79)

The chloropyridine (22g) was added to dry methanol (150cm^3) containing sodium (5g). The mixture was refluxed for 5 hours and the resulting red solution cooled and filtered. The solvent was then evaporated and the gum partitioned between chloroform and water. The chloroform layer was dried and evaporated to yield a red oil which was distilled under 4mm pressure at 57^{0}C (16g, 75%). m/e 137 (M^+) and 106 (base); ν max 1100(OMe) and 2800cm^{-1}; δ ($CDCl_3$), 1.45 (3H, d, CH_3), 3.30 (3H, s, OCH_3), 4.42 (1H, q, CH), 7.3 (1H, m, 5-H), 7.7 (1H, m, 4-H), 8.65 (1H, m, 6-H) and 8.80 (1H, m, 2-H).

Ethyl acetimidate hydrochloride

Acetonitrile (105g) (dried by distillation over phosphorous pentoxide) was mixed with absolute alcohol (119g) and sodium dried ether (170cm^3). Dry hydrogen chloride gas was passed through the mixture, maintained under anhydrous conditions, and cooled in an ice bath at 10^{0}C. When 1mol. equivalent of hydrogen chloride had been absorbed (a weight increase of 83g ~4h), the solvents were removed by evaporation under reduced pressure. The crystalline product which had formed was collected and washed with ether. This hydrochloride was stored in a desiccator over potassium hydroxide and phosphorous pentoxide. (273.3g, 86.4%), m.p. 300^0, ν max 1640cm^{-1}.

1-Ethoxy-1-oximidoethane (93)

50g of ethyl acetimidate hydrochloride was added, with cooling, to a solution of potassium carbonate (112g) in water (250cm^3). The mixture was then shaken for 10 minutes at room temperature and the product separated out as a colourless oil. The aqueous phase was removed and extracted with ether and these portions together with the product mixed and cooled in an ice salt bath. A solution of hydroxylamine hydrochloride (30.2g) in water (125cm^3) was added and the mixture shaken for 15 minutes. The ether layer was removed and the aqueous layer extracted with ether. The ether layers were combined, dried and the solvent removed to yield a colourless oil. (22g, 51%): ν max 3600 - 3,200, 1665, 1300 and 1050:δ($CDCl_3$), 1.15 (3H, t, $C\underline{H}_3$ -CH_2), 1.86 (3H, s, $C\underline{H}_3$-C), 3.90 (2H, q, $C\underline{H}_2$-CH_3) and 8.5 (1H, sbr, O$\underline{H}$).

Mesitylene Sulphonyl Chloride

To chlorosulphonic acid (292g) stirred at 0 - 5^0 was added mesitylene (100g) at such a rate that the temperature did not rise above 20^0. After completion (3h) the mixture was stirred for 1 hour and poured into ice. The solid which formed was extracted with carbon tetrachloride which was washed with sodium carbonate solution and then dried. On removal of the solvent an oil was left which crystallised on standing, these were filtered and washed with petrol to yield the title compound (147.9g 80.5%), m.p. 50 - 52^0, ν max 1600, 1580, 1360, 1180 and 1170 (SO_2), 850, 780 and 740cm^{-1}.

Ethyl-o-mesitylenesulphonylacetohydroxamate (94)

The oxime (93) (20g) and dimethylformamide (100cm^3) was added to triethylamine (21.7g 16cm^3). Then mesitylenesulphonyl chloride (42.4g) was added over a 40 minute period, keeping the temperature below 18^{0}C. The mixture was stirred for 1 hour and poured onto ice. After stirring for a few minutes, a white solid precipitated out, this was filtered and washed with petrol. The yield of this pure compound was (47.3g. 85.6%) m.p. 48 - 50^{0}C (dec.) ν max 1645(C=N), 1360 and 1180 (SO_2O)cm^{-1}; δ ($CDCl_3$), 1.2 (3H, t, $\underline{CH_3}$-CH_2), 2.1 (3H, s, $\underline{CH_3}$-C-), 2.3 (3H, s, $\underline{CH_3}$-Ar), 2.70 (6H, s, 2xAr-$\underline{CH_3}$), 3.95 (2H, q, $\underline{CH_2}$-CH_3) and 6.95 (2H, s, 2xAr-$\underline{H}$).

O-Mesitylene Sulphonyl hydroxylamine (M.S.H.) (92)

20g of the above product was added to perchloric acid (70%, 60cm^3) and the mixture warmed to 35^0 for 2 minutes. This solution was then stirred for 20 minutes at room temperature. While this reaction was proceeding, water (800cm^3) and 1N sodium bicarbonate solution (125cm^3) were being cooled to 0^{0}C.

After completion of the reaction the brown solution was poured into ice water and the solid filtered after standing for 3 minutes. The solid was washed with the bicarbonate solution and then with the water. The product was then dissolved in ether dried and evaporated at less then 30^0 to yield a white solid. (10.3g, 68.5%) ν max 3,270 and 3,230 (NH_2), 1365 and 1170 (SO_2O)cm^{-1}.

1-amino-3-[1-(methoxy)ethyl]pyridinium mesitylenesulphonate (87)

3-(1-methoxyethyl)pyridine (20g) was cooled in an ice bath and then dissolved in dichloromethane (45cm^3) at 0^{0}C. One mol. of M.S.H. (31.4g) was also dissolved in dichloromethane (90cm^3) and cooled to 0^{0}C.

The two solutions were quickly mixed, portion wise and stirred for 30 minutes in an ice bath. This mixture was then poured into 500cm^3 of ice cold dry ether and stirred for 90 minutes, during which time a yellow oil had formed. The ether was poured off and evaporated down to yield more yellow oil which was combined with rest to yield (42.7g, 83%) of the title compound. ν max 3230 and 3134 (NH_2) and 1190cm^{-1}; δ ($CDCl_3$) 1.3 (3H, d, $C\underline{H}_3$-C), 2.2 (3H, s, $C\underline{H}_3$-Ar), 2.6 (6H, s, 2xAr-$C\underline{H}_3$), 3.2 (3H, s, $OC\underline{H}_3$), 7.6 (1H, m, 5-$\underline{H}$), 7.9 (1H, m, 4-$\underline{H}$), 8.8 (1H, m, 6-$\underline{H}$) and 8.9 (1H, m, 2-$\underline{H}$).

3-[1-(methoxy)ethyl]pyridine-N-acetylimide (88)

The yellow oil from the previous experiment (37.2g) was dissolved in water (60cm^3) and cooled at 5^{0}C. Acetic anhydride (150cm^3) previously cooled to 5^{0}C was added and the whole reaction stirred for 15 minutes. A solution of 50% potassium carbonate was added drop-wise, maintaining the temperature at 5^{0}C, until just basic. The solution was then extracted with chloroform, dried and evaporated down to yield a dark brown oil (16.1g, 84.7%). ν max 1580 (C=O)cm^{-1}.

1-(N-methylacetamido)-3-[1-(methoxy)ethyl]pyridinium iodide (89)

Methyl iodide (60cm^3) was quickly added to the acetylated product and the mixture refluxed for 45 minutes. Excess methyl iodide was removed to yield a dark viscous oil which slowly crystallised, affording cubes of the methiodide (27.4g, 95%). ν max 1700 (C=O)cm^{-1}; δ ($CDCl_3$ & $(CD_3)_2SO$), 1.56 (3H, d, J 6Hz $C\underline{H}_3$-CH), 2.40 (3H, s, $C\underline{H}_3$-N), 3.40 (3H, s, $C\underline{H}_3$-O), 4.92 (3H, s, $C\underline{H}_3$-CO), 4.78 (1H, q, $C\underline{H}$-CH_3), 8.32 (1H, m, 5-$\underline{H}$), 9.40 (1H, m, 6-$\underline{H}$) and 9.46 (1H, m, 2-$\underline{H}$).

3-[1-(methoxy)ethyl]pyridine-4-carbonitrile (90)

The methiodide (10g) was dissolved in warm water ($15cm^3$) and a mixture of potassium cyanide (2.4g) and ammonium chloride (2.9g) was then added portion wise over 8 minutes and the solution stirred for a further hour. This mixture was extracted with chloroform ($2 \times 20cm^3$) and the organic phase dried and removed to yield a dark brown oil. This oil was dissolved in absolute ethanol ($200cm^3$) and stirred for 1 hour under soft ultraviolet light. After this, the ethanol was removed and the dark brown residue partitioned between chloroform and water. The chloroform layer was washed well with water, dried and the solvent removed under pressure to yield a brown oil. This oil was then passed down a basic alumina column and eluted with diethyl ether to produce an almost colourless oil of the title compound. (3.2g, 66.2%) m/e 162 (M^+), 147 (base), 131 and 122; λ max (ε) 282 (13,380)nm, υ max 2220(C=N), 1590 and 1570 (pyridine), 1110 and 995 (OCH_3)cm^{-1}; δ ($CDCl_3$) 1.5 (3H, d, CH_3-CH), 3.3 (3H, s, OCH_3), 4.7 (1H, q, CH-CH_3), 7.6 (1H, d, J 7Hz 5-H), 8.7 (1H, d, J 7Hz 6-H), and 8.8 (1H, s, 2-H).

4-(1-iminoethyl)-3-[1-(methoxy)ethyl]pyridine (91)

The carbonitrile (3.0g) was reacted with 1.2 mol. of methyl lithium (0.486g) under nitrogen and the solution stirred for 30 minutes. Aqueous ammonium chloride was slowly added and then the solution was extracted with chloroform which was dried, and evaporated to yield a dark brown oil (2.8g, 85%). υ max 1650 (C=N)cm^{-1}.

4-Acetyl-3 [1-(methoxy)ethyl] pyridine (17)

The amine (2.5g) was dispersed in acetic acid (60%, 20cm^3) and stirred for 30 minutes at room temperature. The dispersion was cooled to 5^{0}C and basified with sodium carbonate after which the solution was extracted with chloroform which, on evaporation, yielded a dark brown viscous oil. The oil was purified by eluting with diethyl ether down a basic alumina column to produce a pale amber oil of the desired product (2.1g, 83%). m/e 179 (M^+) and 164 (base); ν max 1700 (C=O), 1256 (CO), 1110 and 1070 (OCH_3)cm^{-1}; δ ($CDCl_3$) 1.34 (3H, d, $C\underline{H}_3$-CH), 2.60 (3H, s, $C\underline{H}_3CO$), 3.36 (3H, s, $C\underline{H}_3O$), 4.41 (1H, q, $C\underline{H}$-CH_3), 7.86 (1H, d, J 7Hz 5-H), 8.71 (1H, d, J 7Hz 6-H), and 8.90 (1H, s, 2-H).

(E) and (Z)-2 [1- [3-(1-methoxyethyl)-4-pyridyl] ethylidene] benzo [f] indolin-3-one (19 & 20)

1,3-diacetylbenzo [f] indoxyl (1.21g) and 4-acetyl-3 [1-(methoxy) ethyl] pyridine (810mg) were dissolved in a 50% aqueous methanol solution (12cm^3, deoxygenated) under nitrogen, containing potassium hydroxide (1.9g).

The solution was set aside for 1 week, after which the solution was swiftly poured into 20% acetic acid (75cm^3) which had been cooled to 5^{0}C. After stirring for 10 minutes a dark blue solid precipitated, this was collected and dried. This solid was then stirred with dichloromethane (20cm^3) for 20 minutes and then filtered once again. Evaporation of the solvent yielded a brown gum and purification of this was carried out on a neutral alumina column and eluting with 10% petroleum ether in ethyl acetate. This yielded a mixture of the (E) and (Z) isomers as a light brown gum which would not crystallise.

(0.625g, 40.1%) m/e 344 (M^+), 312 and 297 (base); υ max 3120 (N-H), 1690, 1685 (CO) and 1640 (C=C)cm^{-1}.

The precipitate which remained after the initial dichloromethane extraction was warmed and stirred with dichloromethane ($20cm^3$) for 10 minutes and filtered once again. After evaporation of the solvent the (E) isomer was obtained as a pale pink solid (0.03g, 2.0%) m.p. 197 (dec.) m/e 344 (M^+), 312 and 297 (base); λ max (ε) 210 (1,032) 235 (1,720), 277 (17,544) and 304 (19,264); υ max 3130 (N-H), 1690 (CO) and 1640 (C=C); δ ($CDCl_3$ & $(CD_3)_2SO$ Fig. 12) 1.28 and 1.44 (3H, 2xd, J 7Hz CH-CH_3), 2.20 and 2.24 (3H, 2 x s, C-CH_3), 3.13 and 3.24 (3H, 2xs, C-OCH_3), 4.4 (1H, q, J 7Hz CH-CH_3), 7.0 (1H, d, J 6Hz 5'-H), 7.18 (1H, s, 4-H), 7.24 (1H, d, J 8Hz 8-H), 7.48 (2H, dd, J 8Hz 6- and 7-H), 7.68 (1H, d, J 8Hz 5-H), 8.00 (1H, s, 9-H), 8.46 (1H, d, J 6Hz 6'-H), 8.68 (1H, s, 2'-H) and 8.76 (1H, s, N-H).

8,9 Benzoellipticine

The mixture of the (E) and (Z) isomers from above was dissolved in 60% aqueous ethanol ($50cm^3$) and heated to 45^0C. Excess sodium borohydride was added over a period of $\frac{1}{2}$ hour and stirring maintained for a further 1 hour (constant u.v. trace). The solvent was removed under reduced pressure and the residue extracted with chloroform. After drying and evaporation of the solvent a light red gum was obtained. This was dissolved in methanol ($50cm^3$) and treated with hydrogen chloride gas for 1 hour, the solvent was removed and the residue extracted with a mixture of chloroform and sodium hydrogen carbonate solution. The organic layer was separated, dried and evaporated to yield a dark brown gum; attempted crystallisation from a variety of solvents failed. Thin layer chromatography showed the presence of three components, the major of which fluoresced blue. This compound was separated using a basic alumina column and eluting with chloroform. The resulting brown oil was solidified by boiling

with diethyl ether to produce an off white amorphous solid (0.176g, 28%), m/e 330 (M^+), 298, 283 (base) and 268; ν max 3155 (N-H) and 1608 (C=C)cm^{-1}.

This amorphous solid was dissolved in 50% hydrobromic acid ($25cm^3$) and heated under reflux until no further change in the u.v. spectrum was observed (c.a. 10h). The solution was then cooled to room temperature and then chilled in an ice bath. The solid which formed was filtered, washed with cold 50% hydrobromic acid and dried. The free base was liberated from this salt by treatment with ammonia, and extracted into chloroform. The chloroform extract, on evaporation yielded a light brown solid which was dissolved in methanol and silica (500mg.) was added. This mixture was stirred under ultraviolet light for 30 minutes. The methanol was then evaporated and the silica washed with dry ether ($10cm^3$). The product was extracted from the silica by warming with a mixture of methanol and ethylacetate (3:1, $25cm^3$) containing a little concentrated ammonia ($2cm^3$). After drying and evaporation of these solvents the light brown solid residue was sublimed at 250^0C under 0.1mm Hg for 3h; this produced 8, 9-benzoellipticine as a yellow solid which crystallised from ethanol as bright yellow micro-crystals (0.008g, 5.1%), m.p. 327-329^{0}C (dec.) m/e 296 (M^+), 281 (base) and 136, λ max ($\mathcal{E}$), 273 (37,900), 309 (30,200), 320 (33,744) and 340 (16,872); δ ($CD_3)_2SO$) 2.8 (3H, s, 5- C<u>H</u>$_3$), 3.64 (3H, s, 13-C<u>H</u>$_3$), 7.48 (2H, m, 8- and 9- <u>H</u>), 7.86 (1H, s, 12- <u>H</u>), 8.12 (3H, m, 3- 4- and 11- <u>H</u>), 8.38 (1H, m, 10- <u>H</u>), 8.90 (1H, s, 7- <u>H</u>), 9.68 (1H, s, 1- <u>H</u>), and 9.72 (1H, s, N-<u>H</u>); (Found C, 85.40; H, 5.51; N, 9.65; $C_{21}H_{16}N_2$ Requires C, 85.14, H, 5.405; N, 9.46%).

3-Acetylbenzo [f] indoxyl (93)

The dark aqueous methanolic solution produced from the condensation between (74) and (17 see page 79) was poured into 20% acetic acid and the solid which precipitated filtered. The clear brown solution was extracted with chloroform (4 x $100cm^3$) and the chloroform dried and evaporated under reduced pressure.

The resulting brown liquid, which smelt of acetic acid was left at room temperature for 24 hours after which crystals had deposited. These were filtered and washed with cold 50% aqueous methanol and then ether to produce brown florets of 3-acetylbenzo [f] indoxyl (27mg, 2.7%) m.p. 207 (dec.) λ max (ε) 268 (20,250), 283 (6,300) and 294 (4,500)nm; ν max 3150 (NH), 1710 (C=O), 1660, 1380, 900, 810 and $740cm^{-1}$; δ ($CDCl_3$ & $(CD_3)_2SO$) 2.22 (3H, s, $COC\underline{H}_3$), 7.38 - 7.60 (2H, m, 5- and 8- $\underline{H}$), 7.68 (3H, m, 2-, 6- and 7-$\underline{H}$), 8.64 (1H, s, 4-$\underline{H}$), 9·00(1H, s, 9-$\underline{H}$) and 12.28 (1H, s, N-$\underline{H}$); m/e 225 (M^+), and 182 (base).

SPECTRA

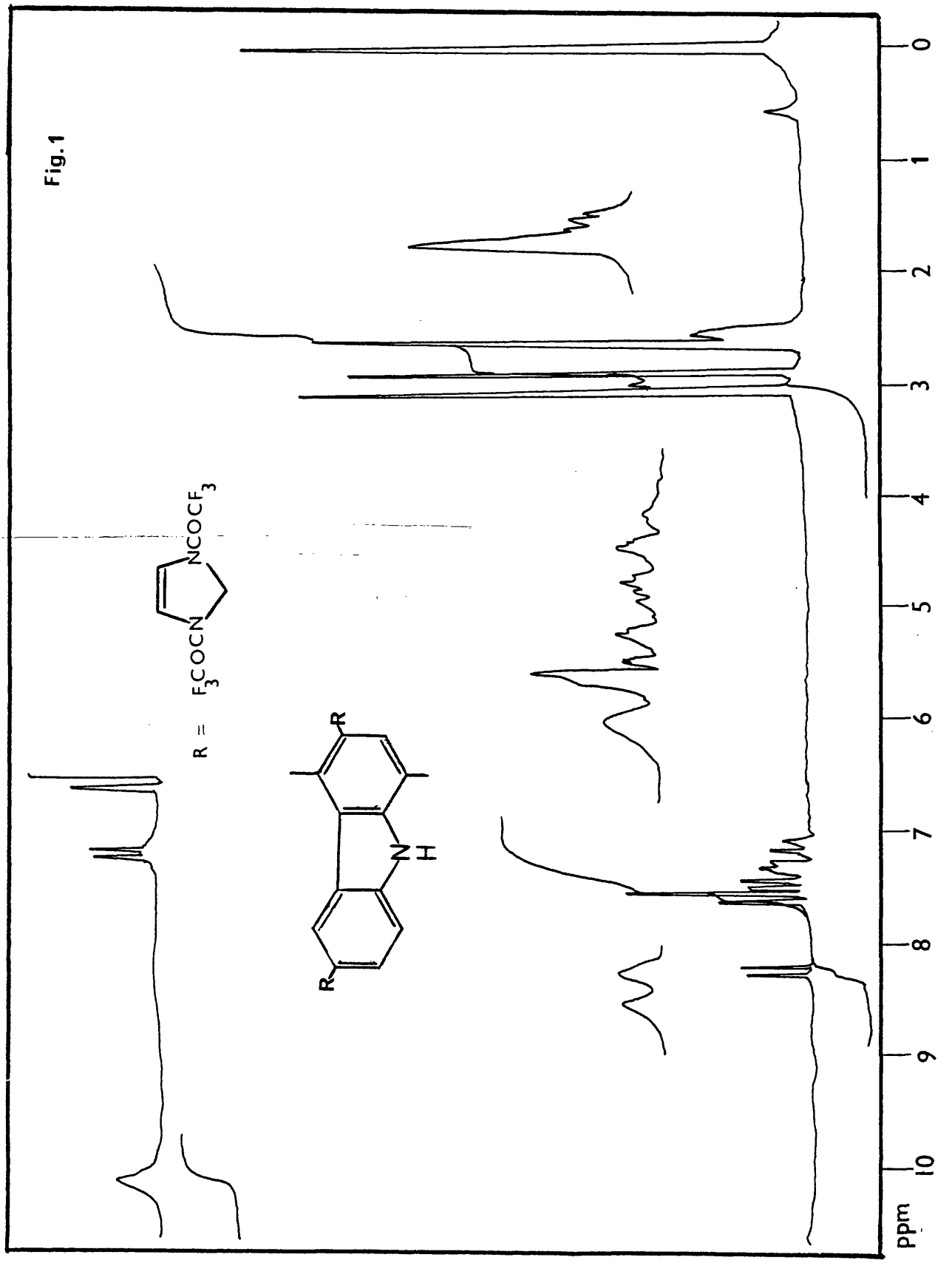
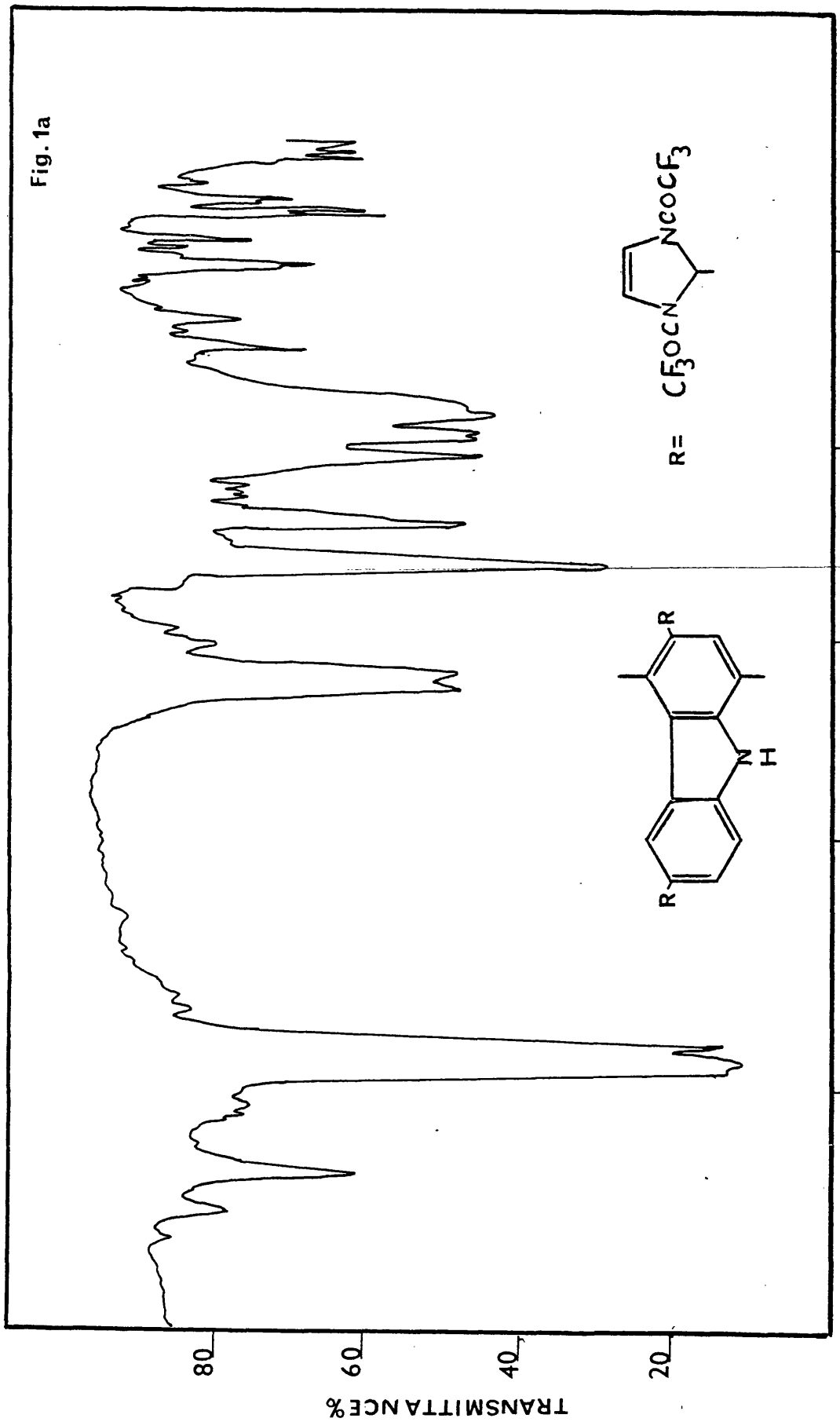


Fig.1

Fig. 1a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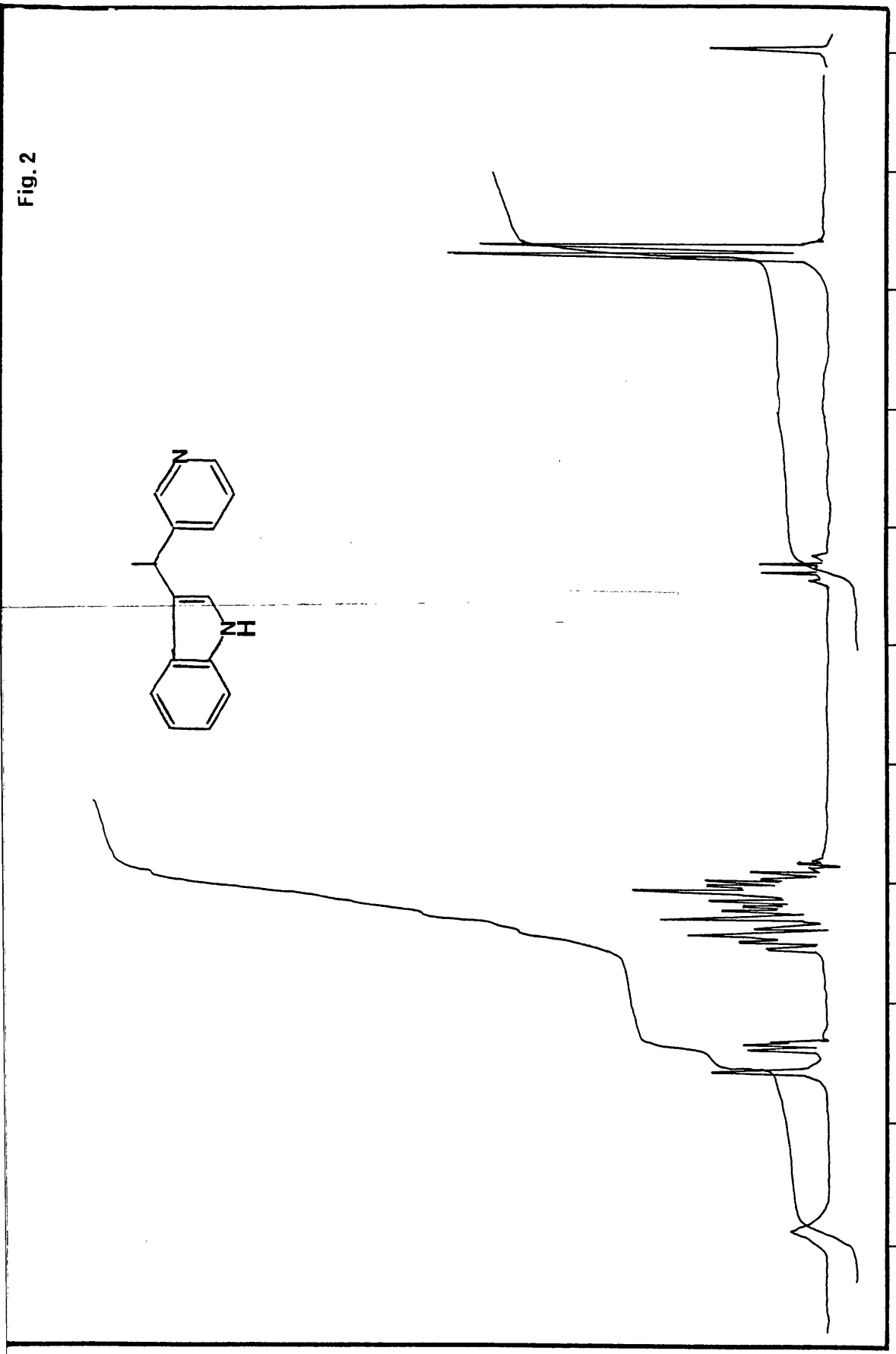


Fig. 2

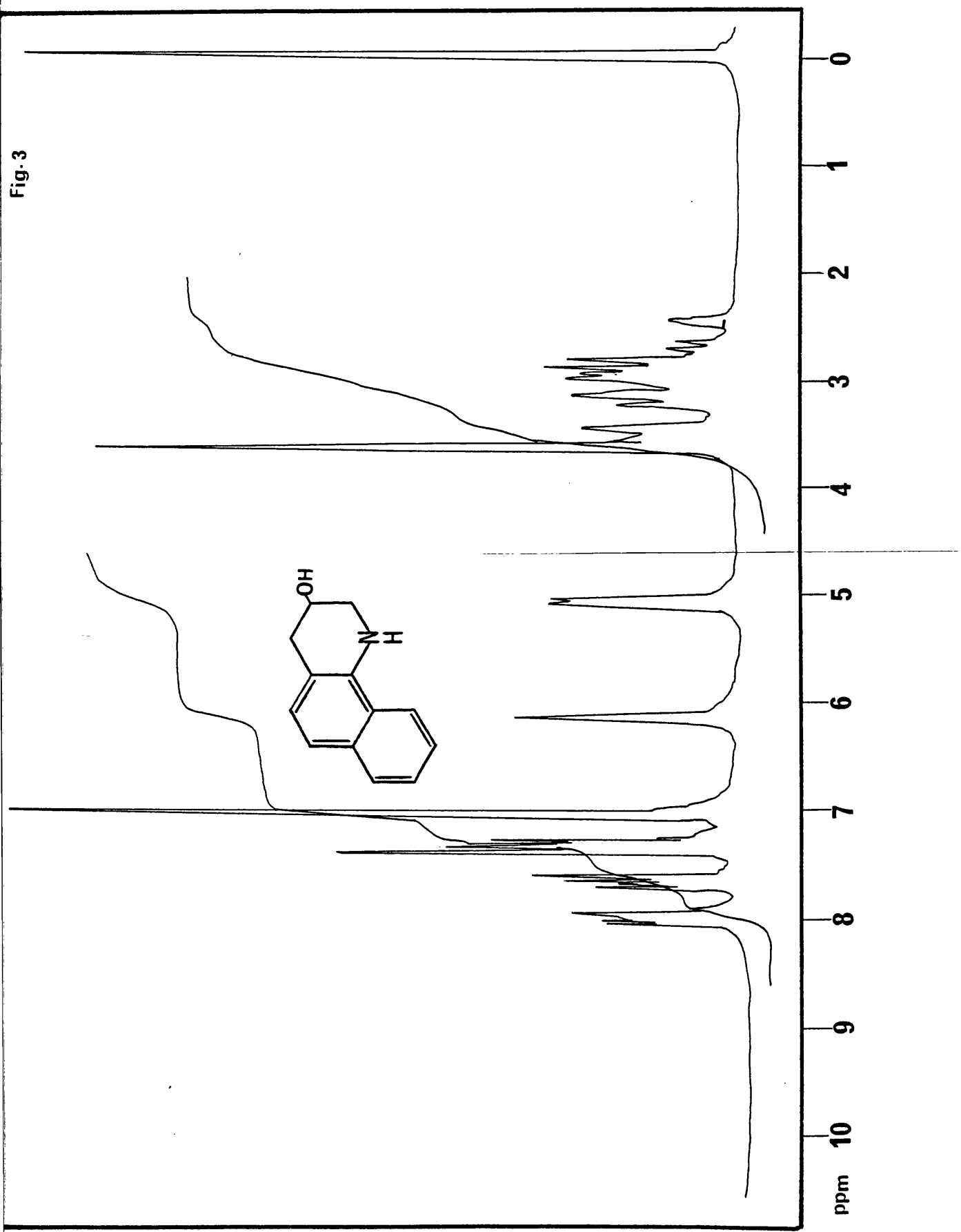


Fig.3

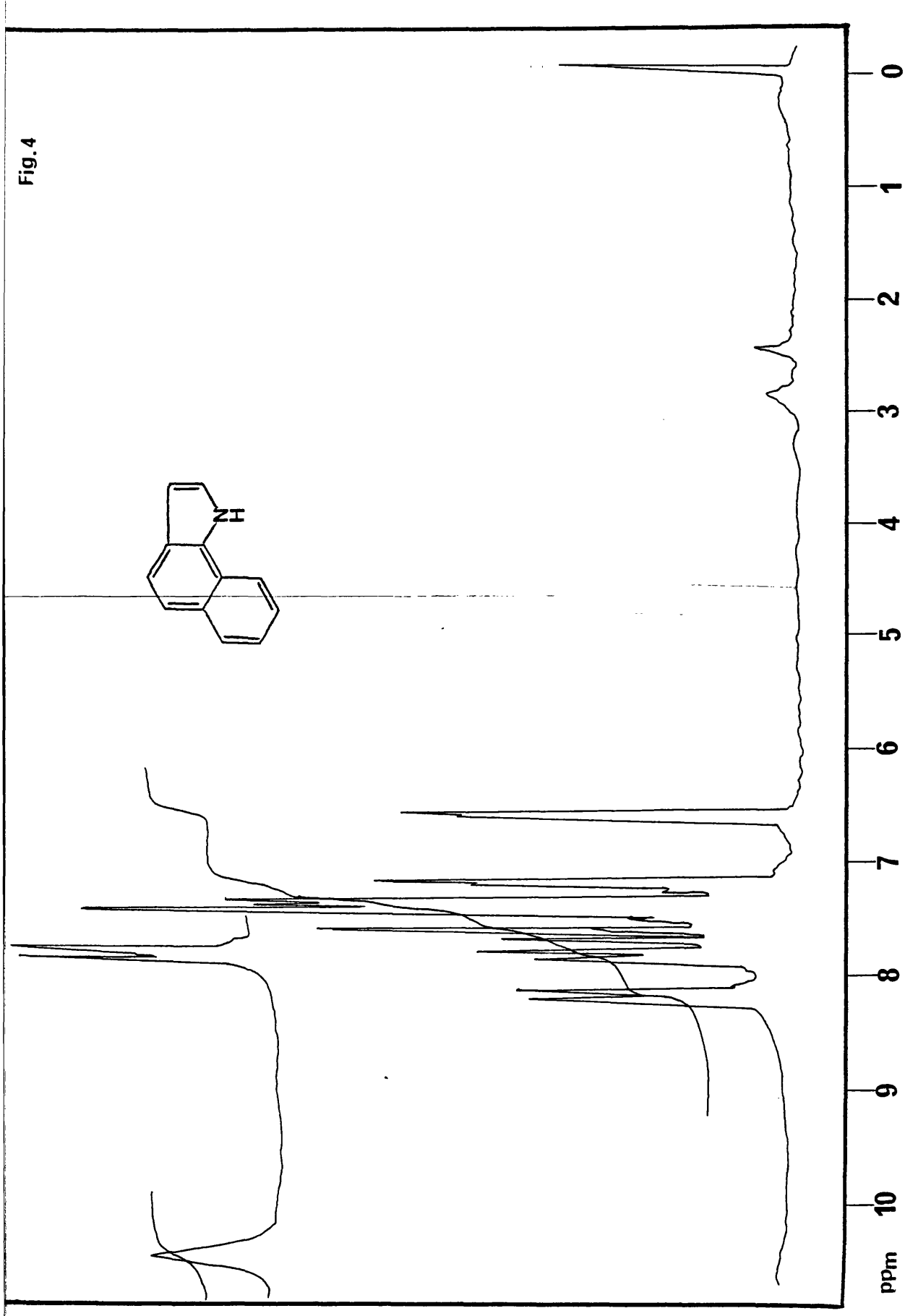
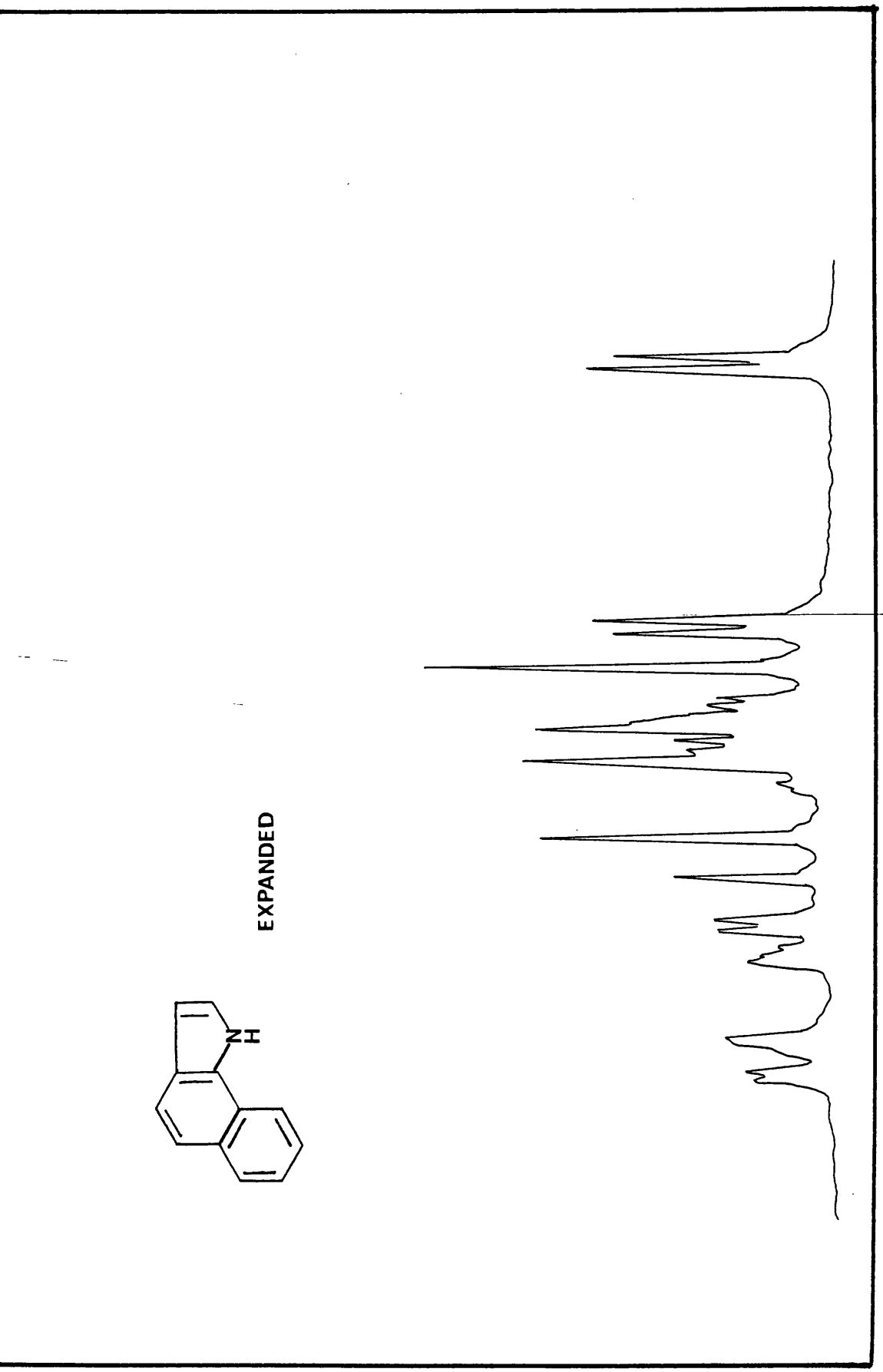


Fig.4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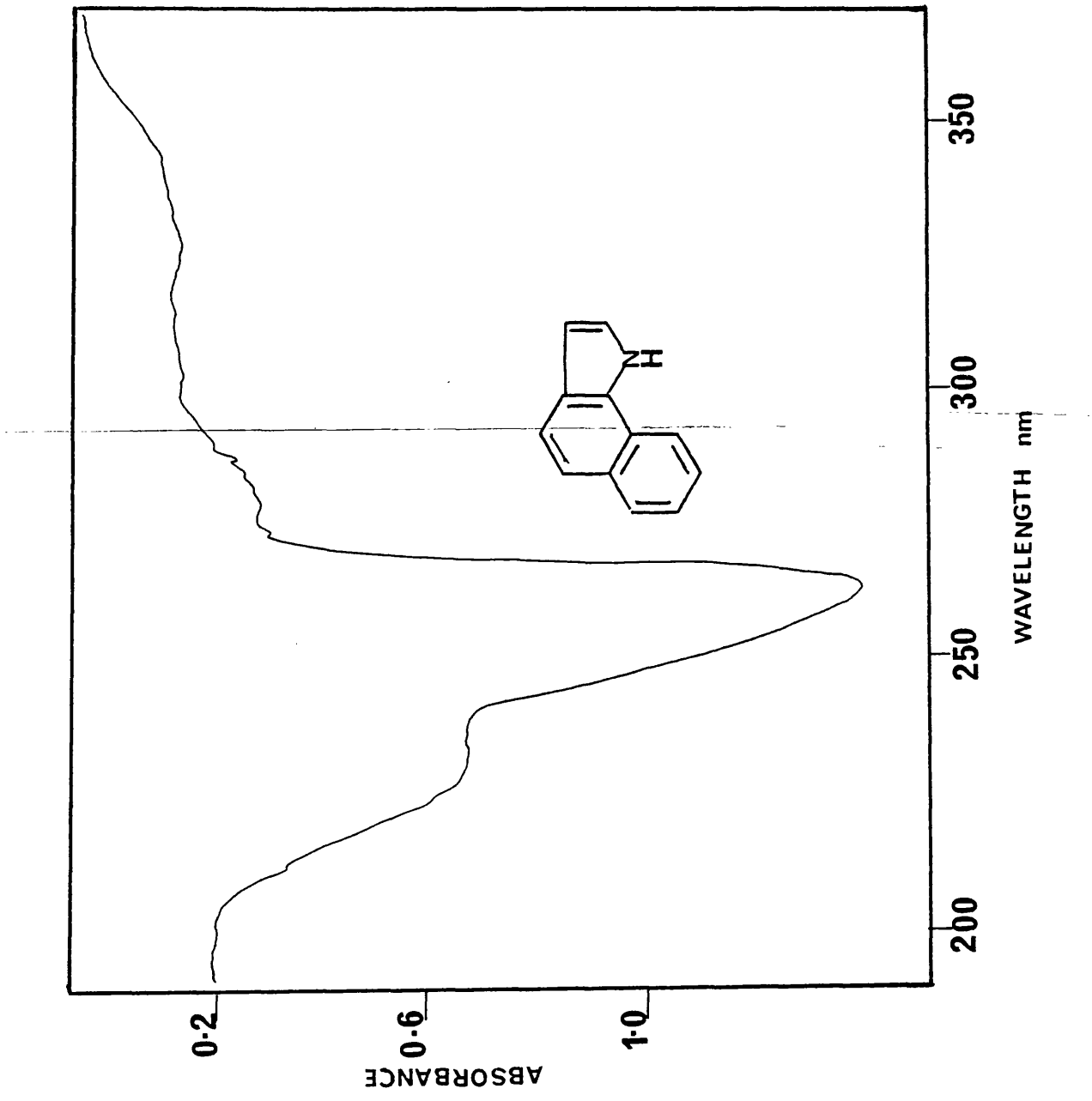
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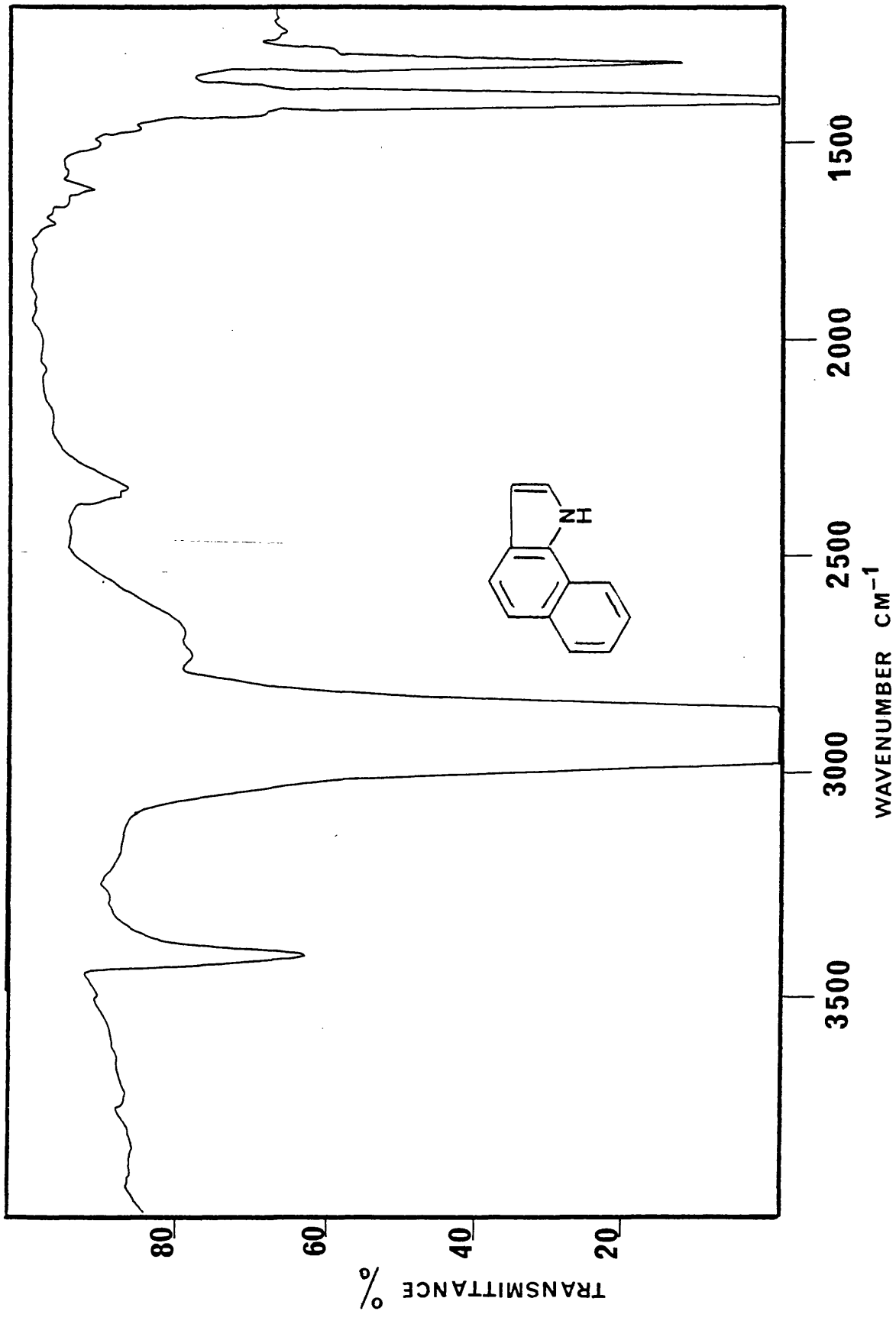
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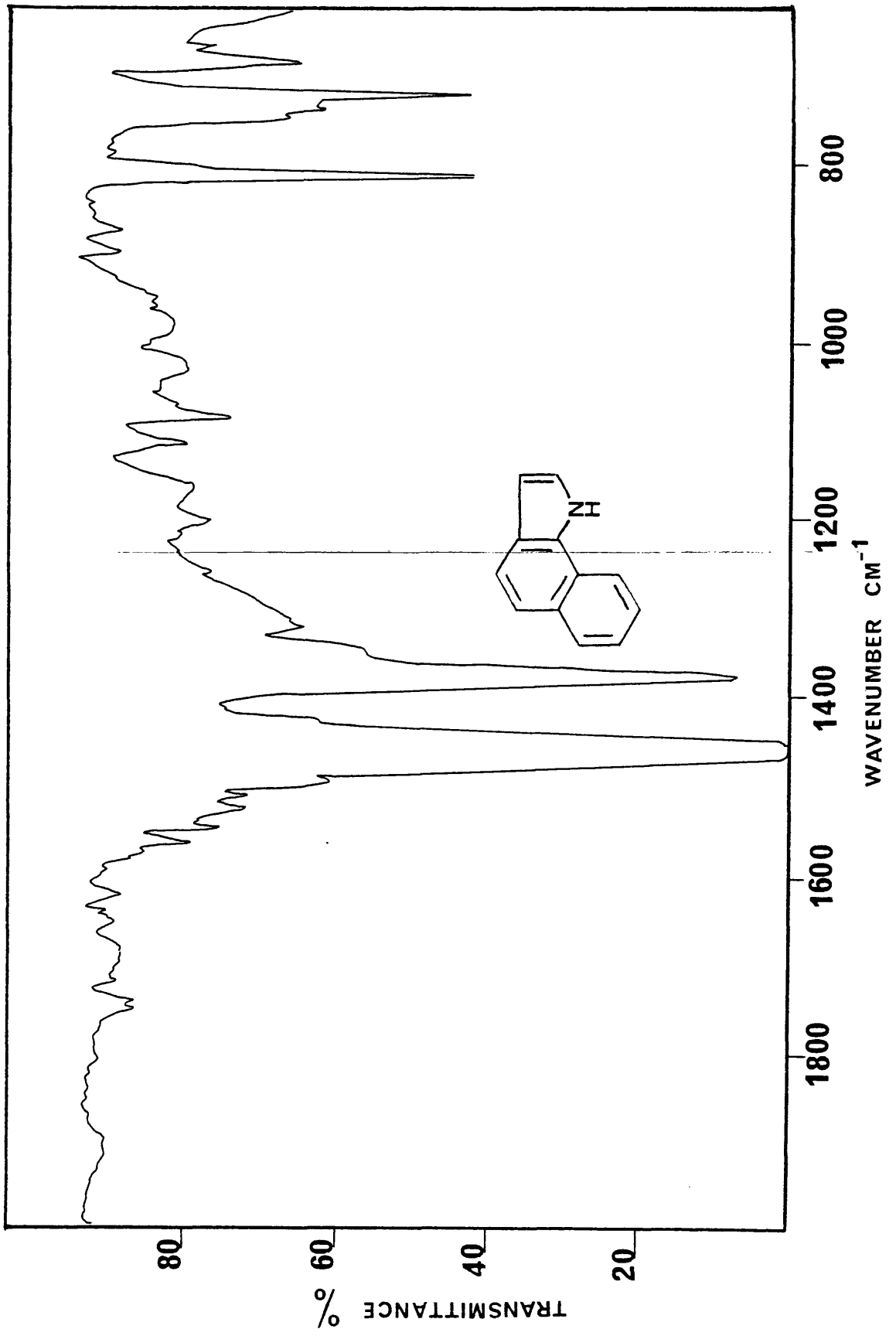
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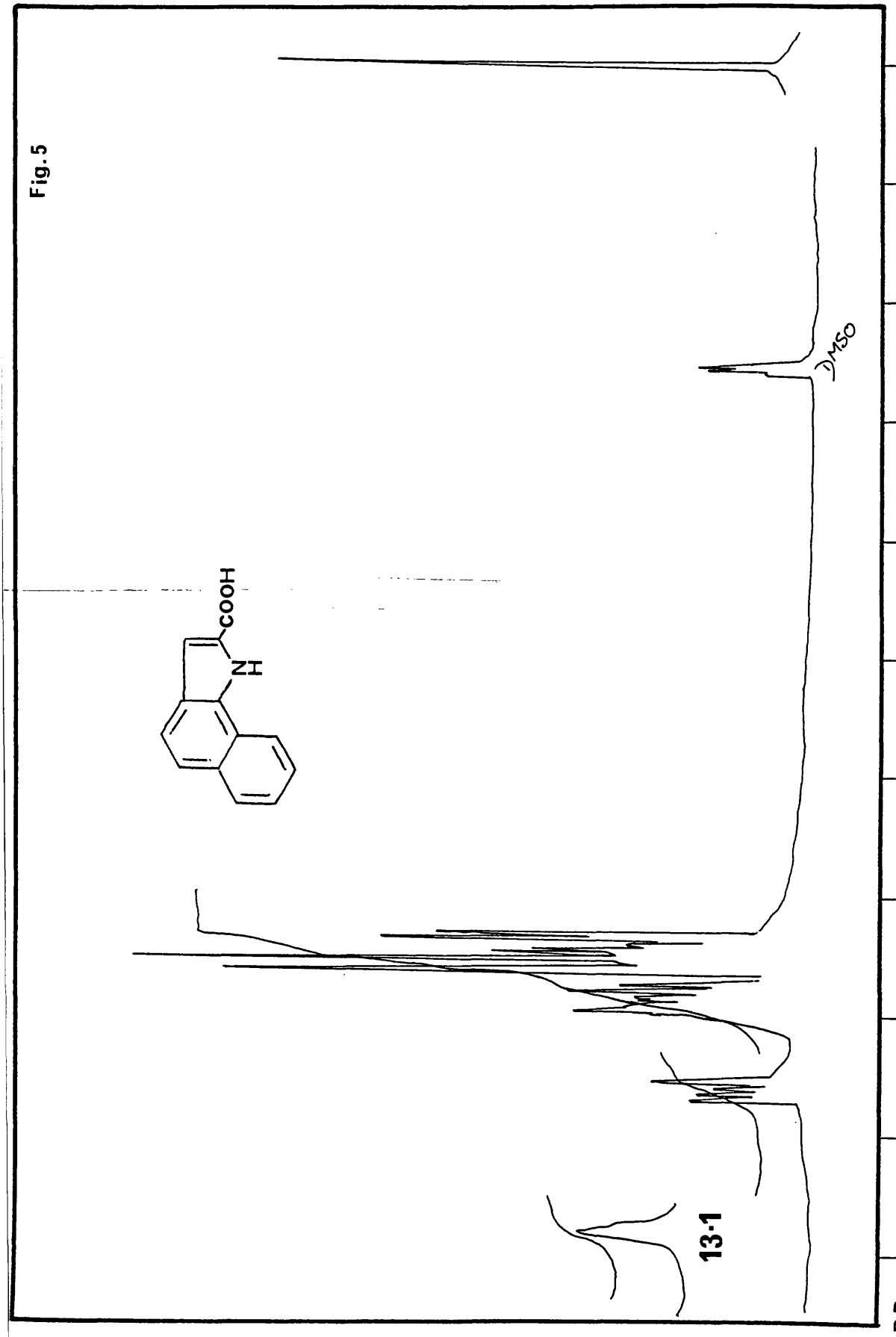
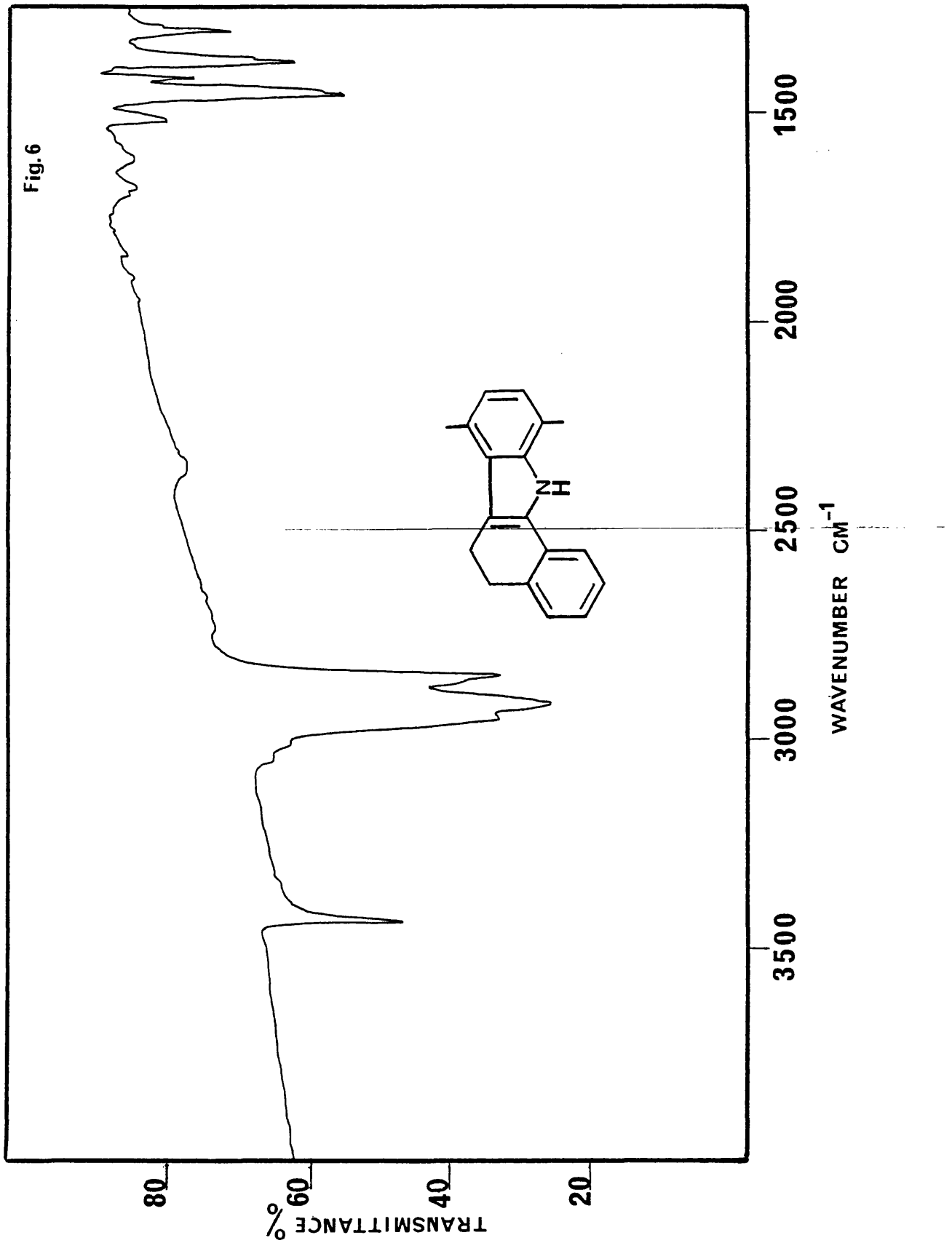


Fig.5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WAVENUMBER CM-1
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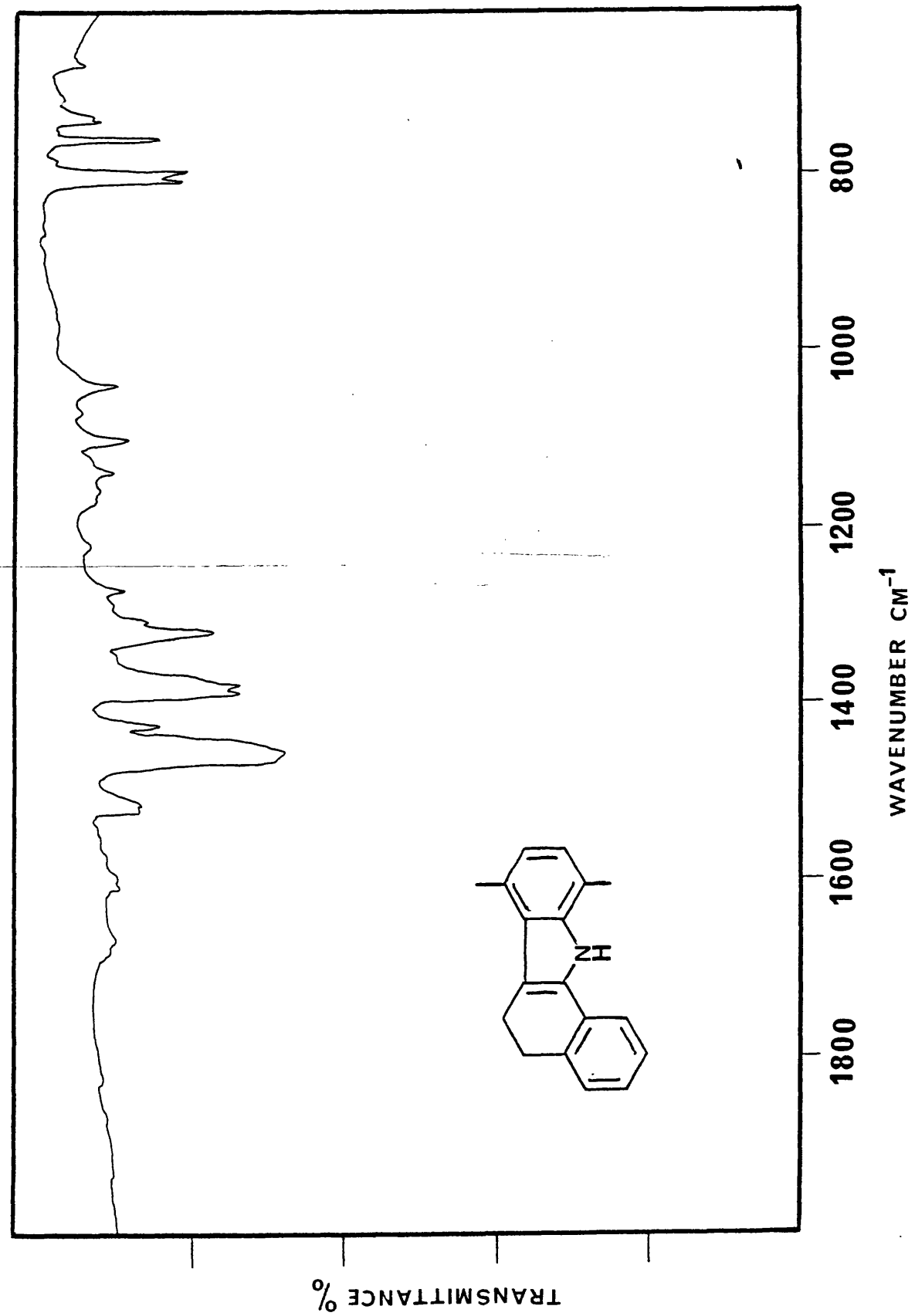
N

Fig.6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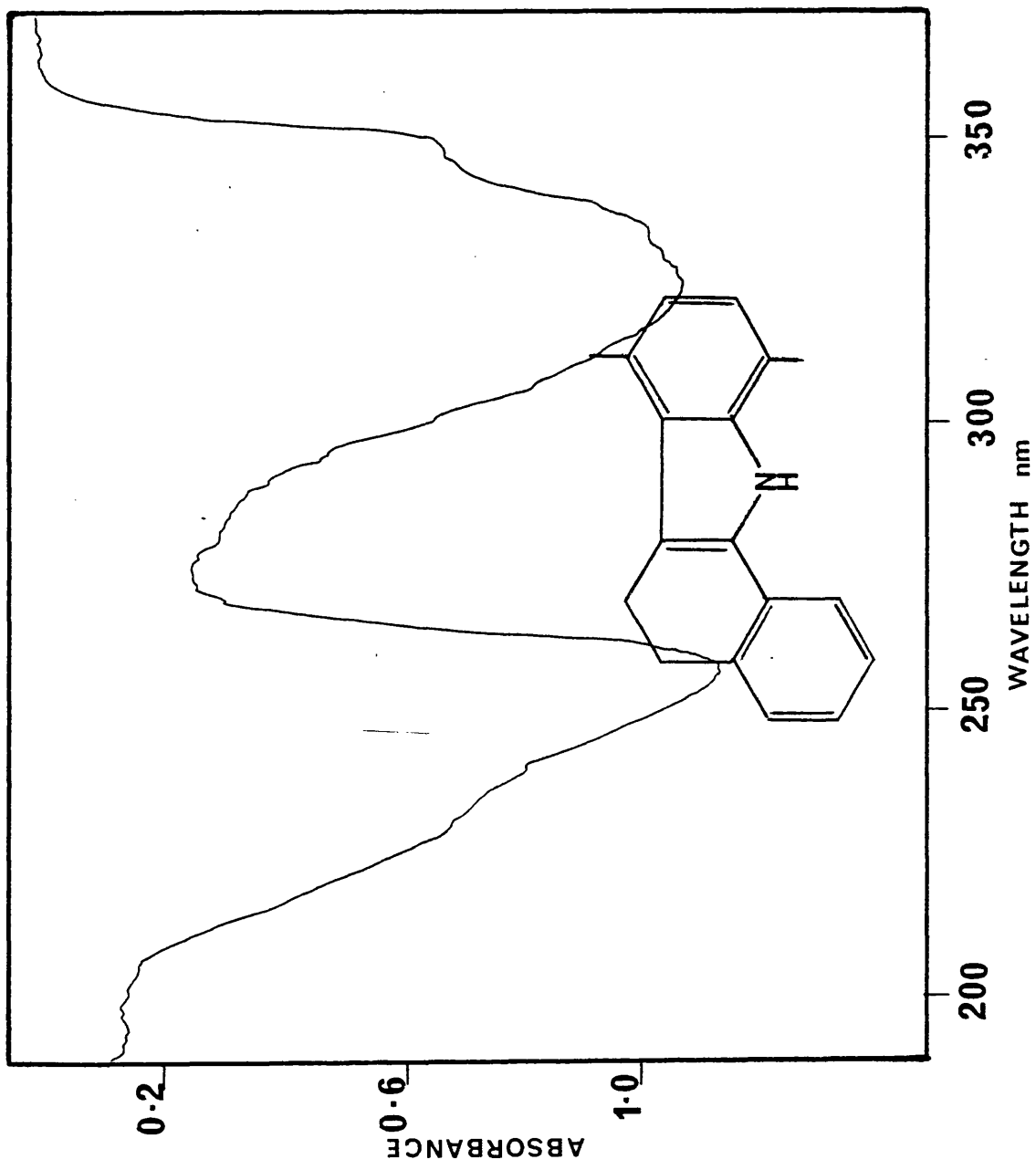
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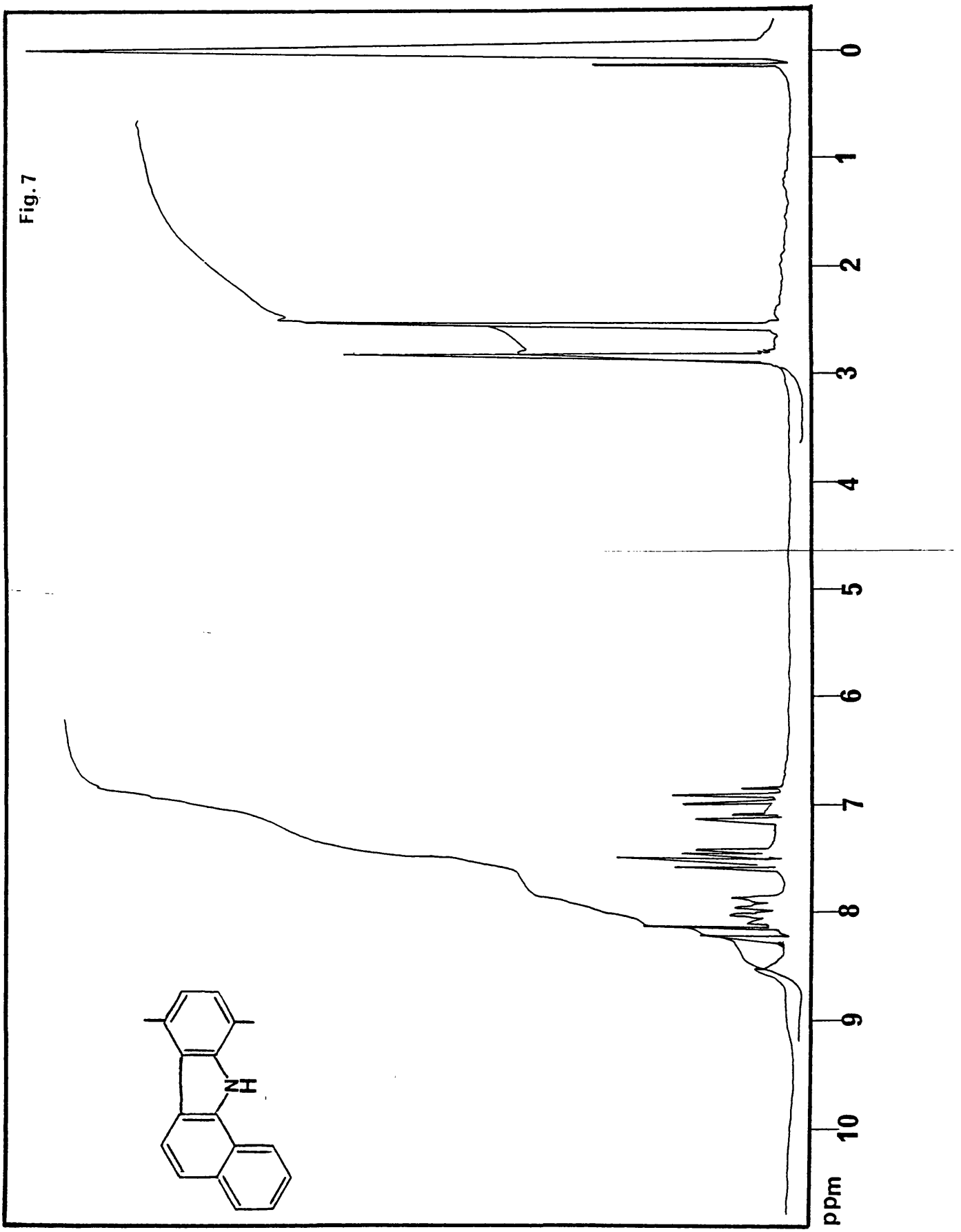
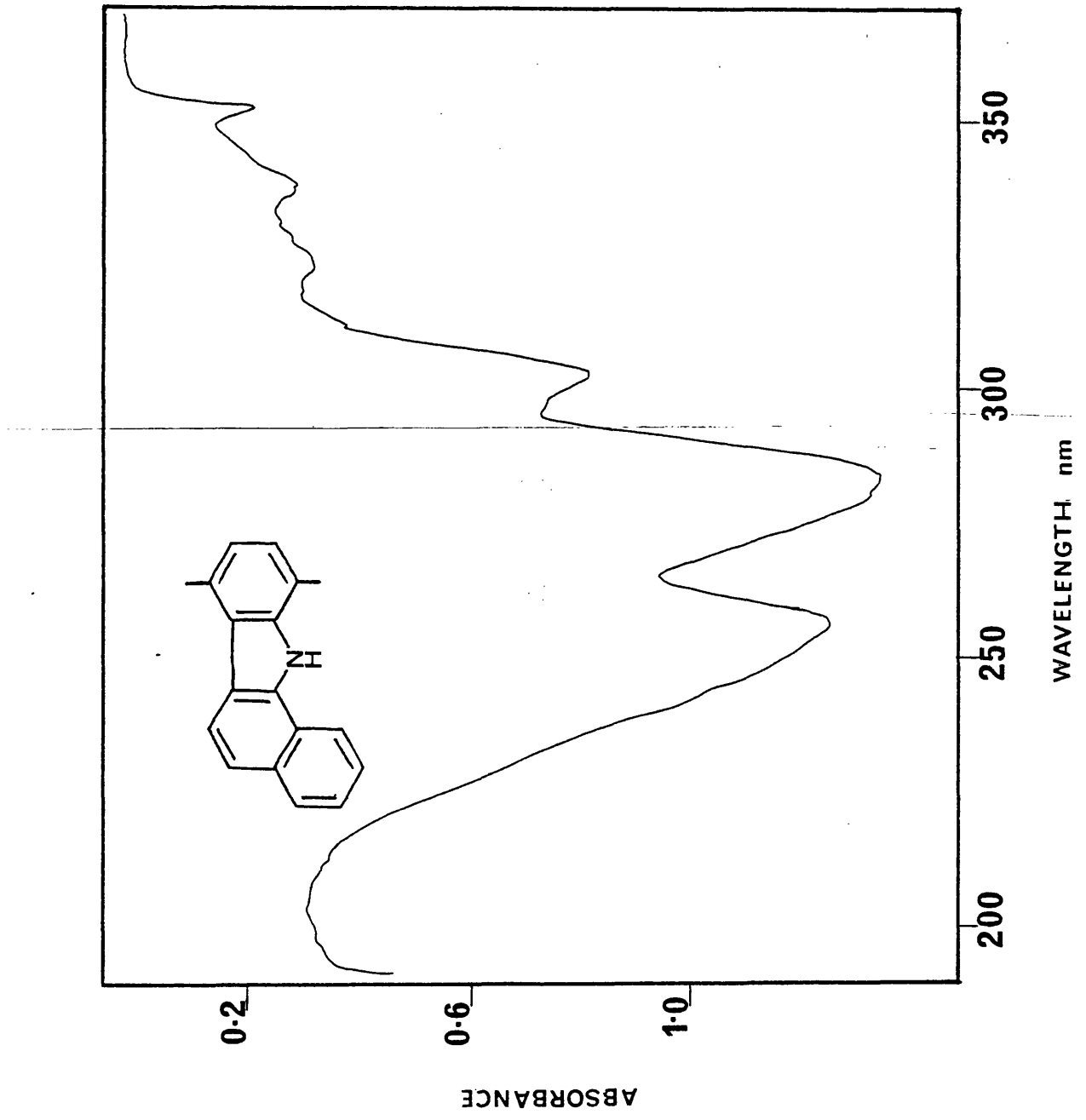


Fig. 7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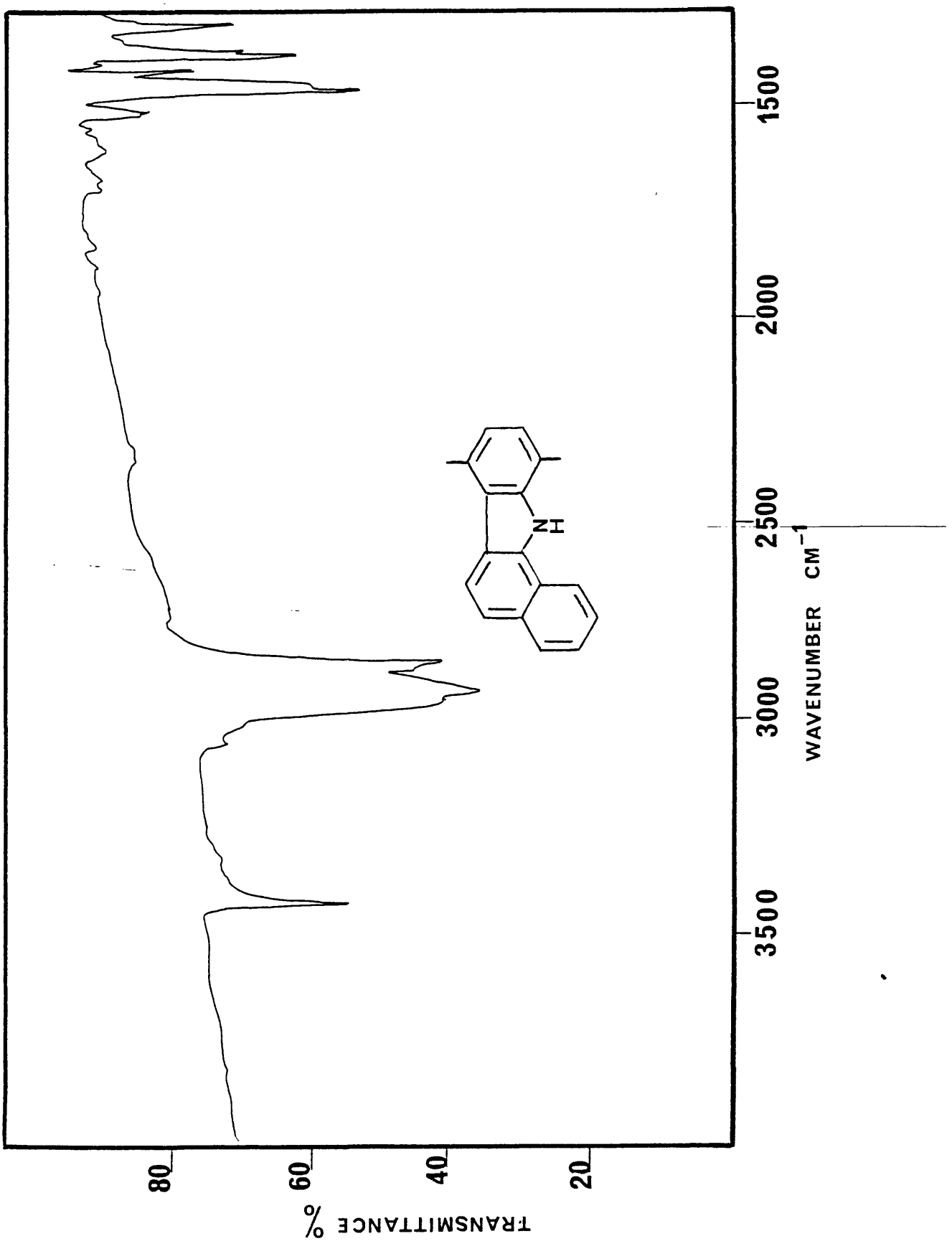
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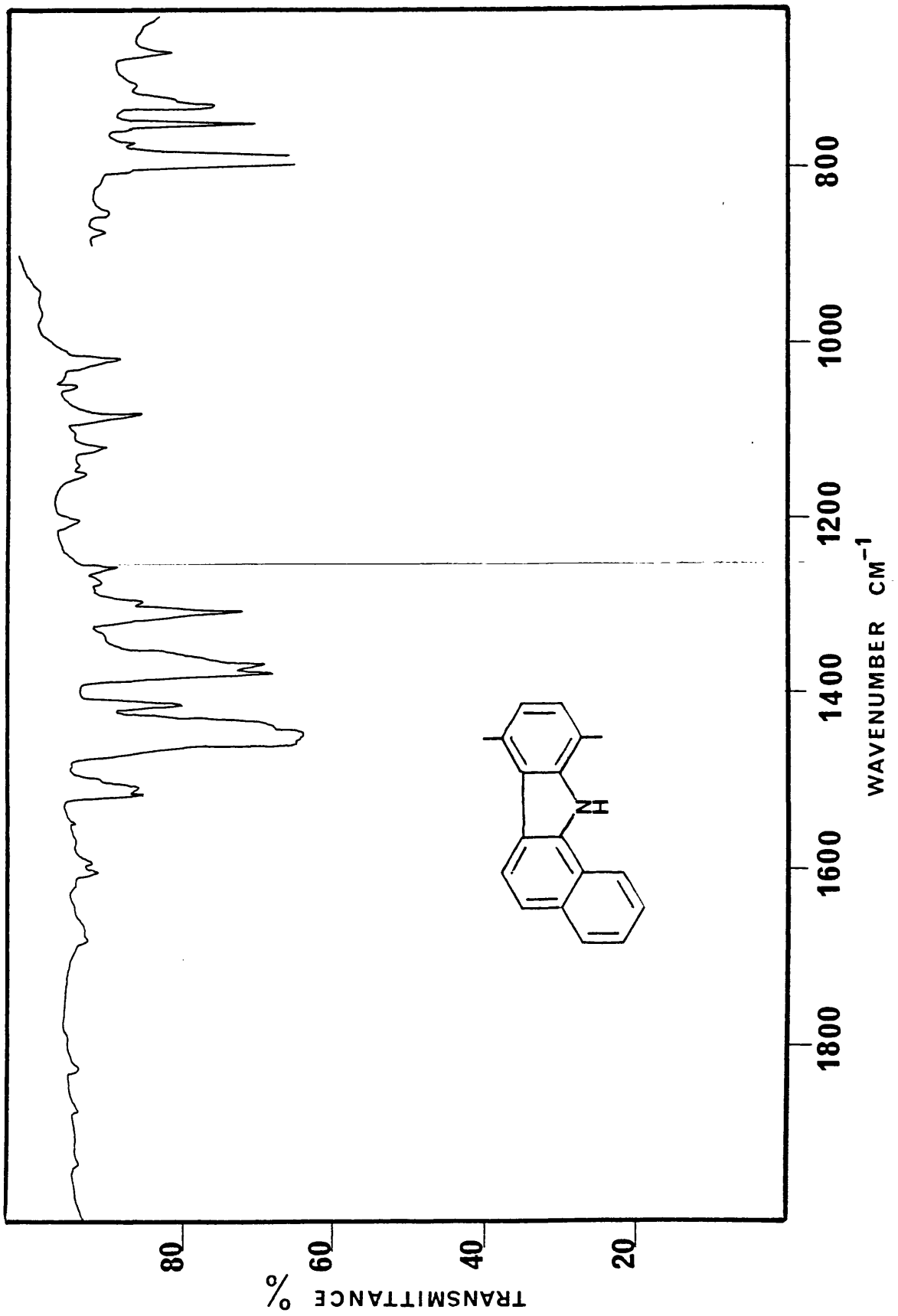
N
H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H
N

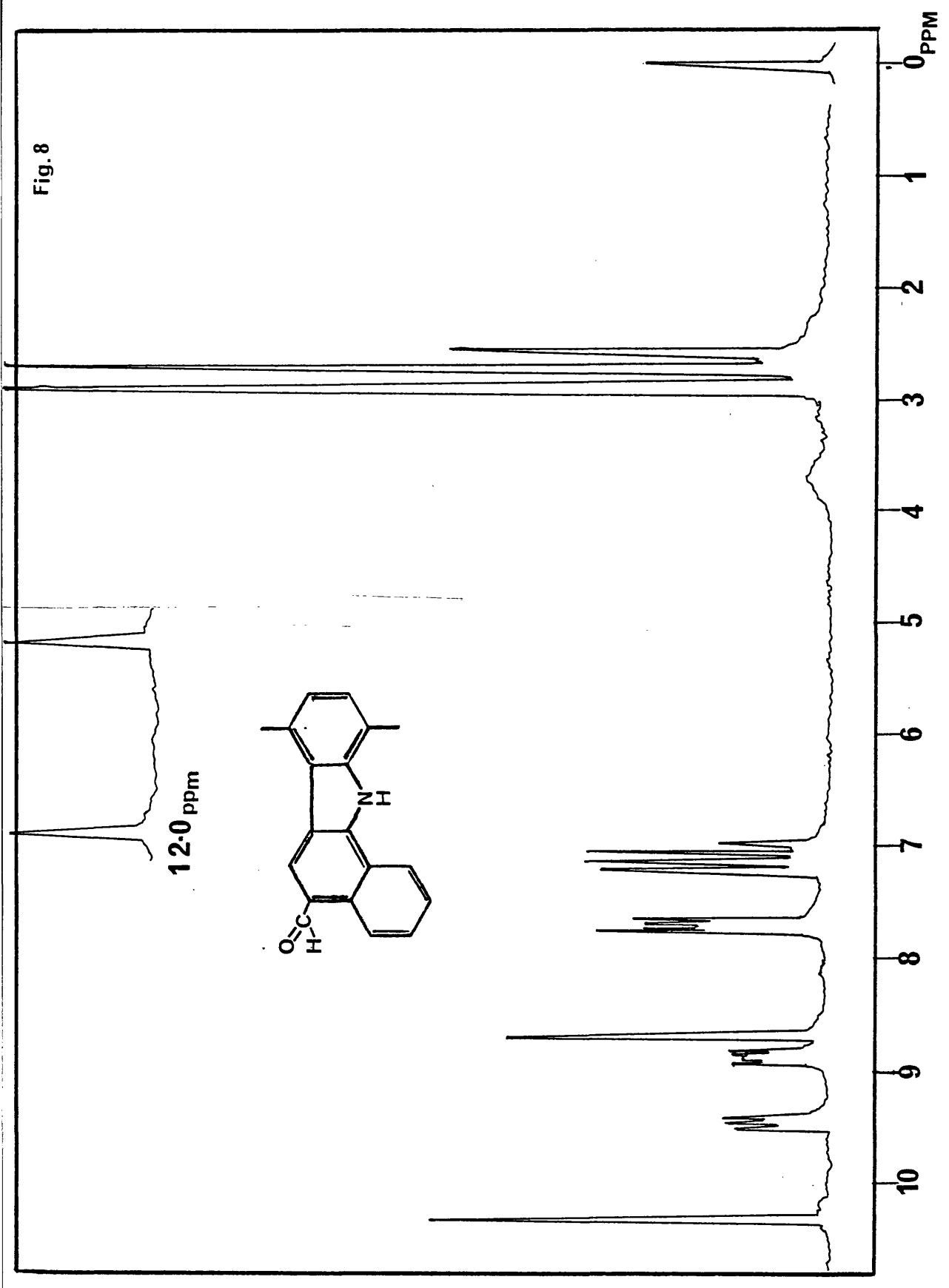
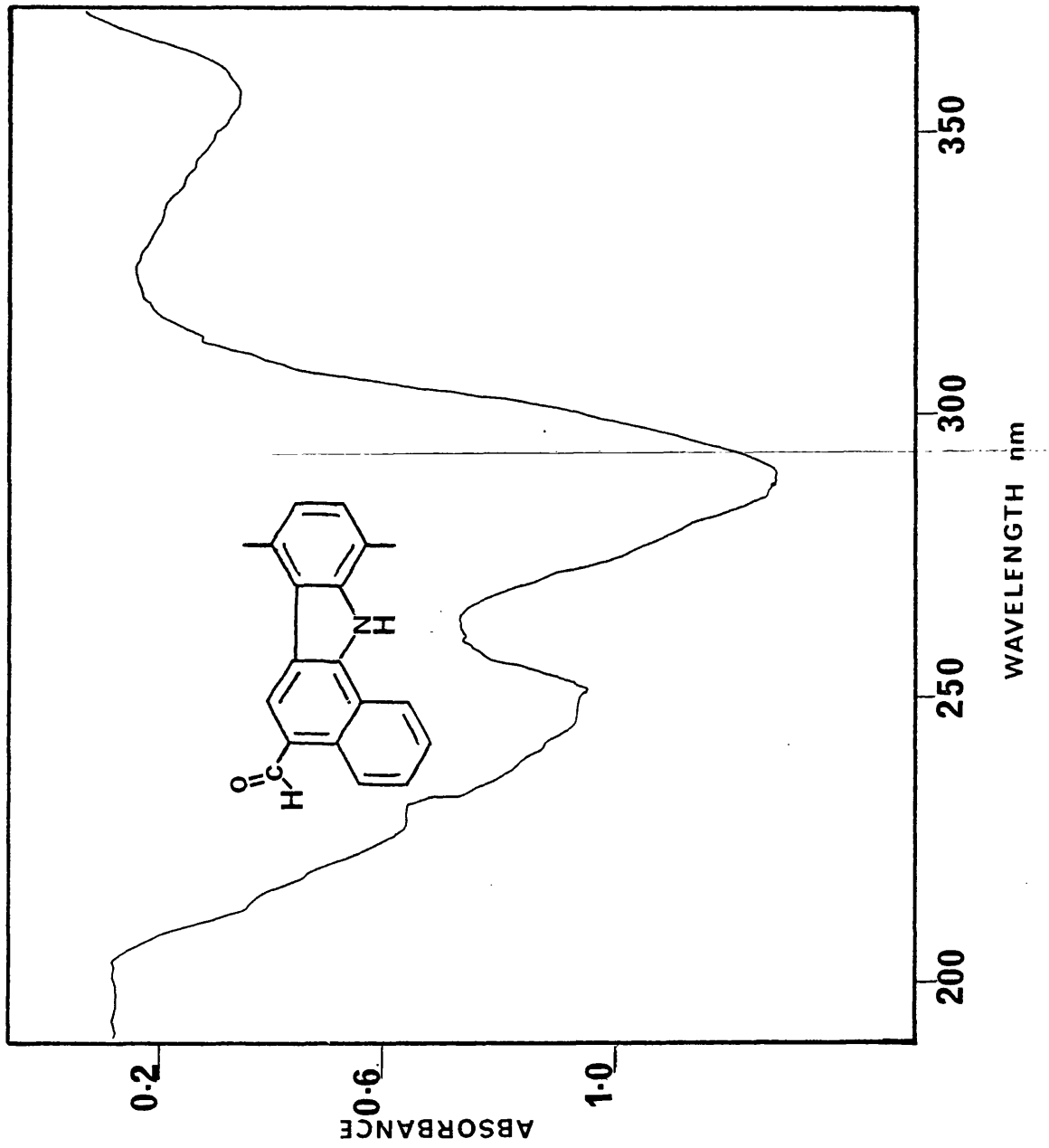


Fig. 8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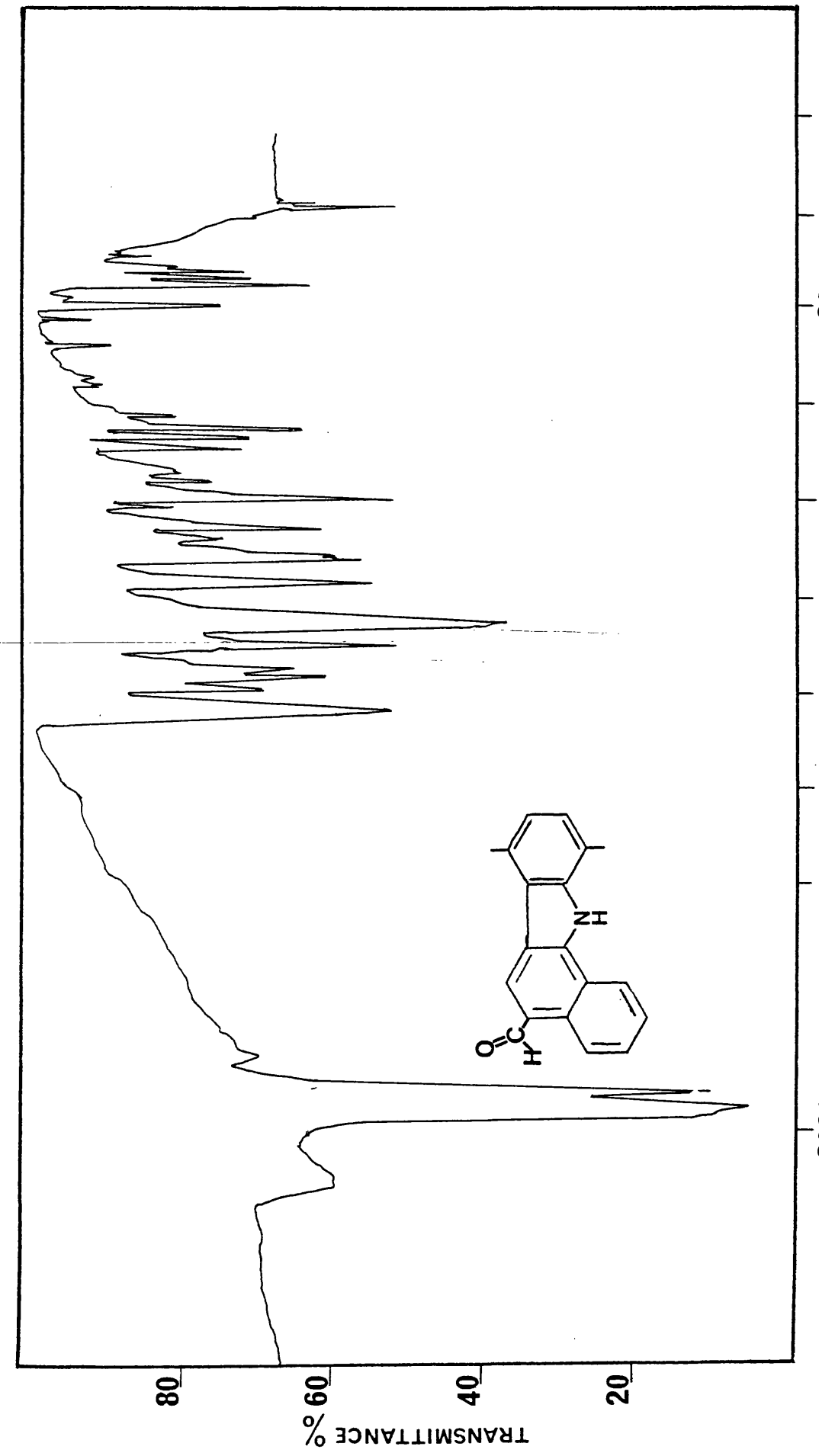
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WAVENUMBER CM^{-1}
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O
C
H

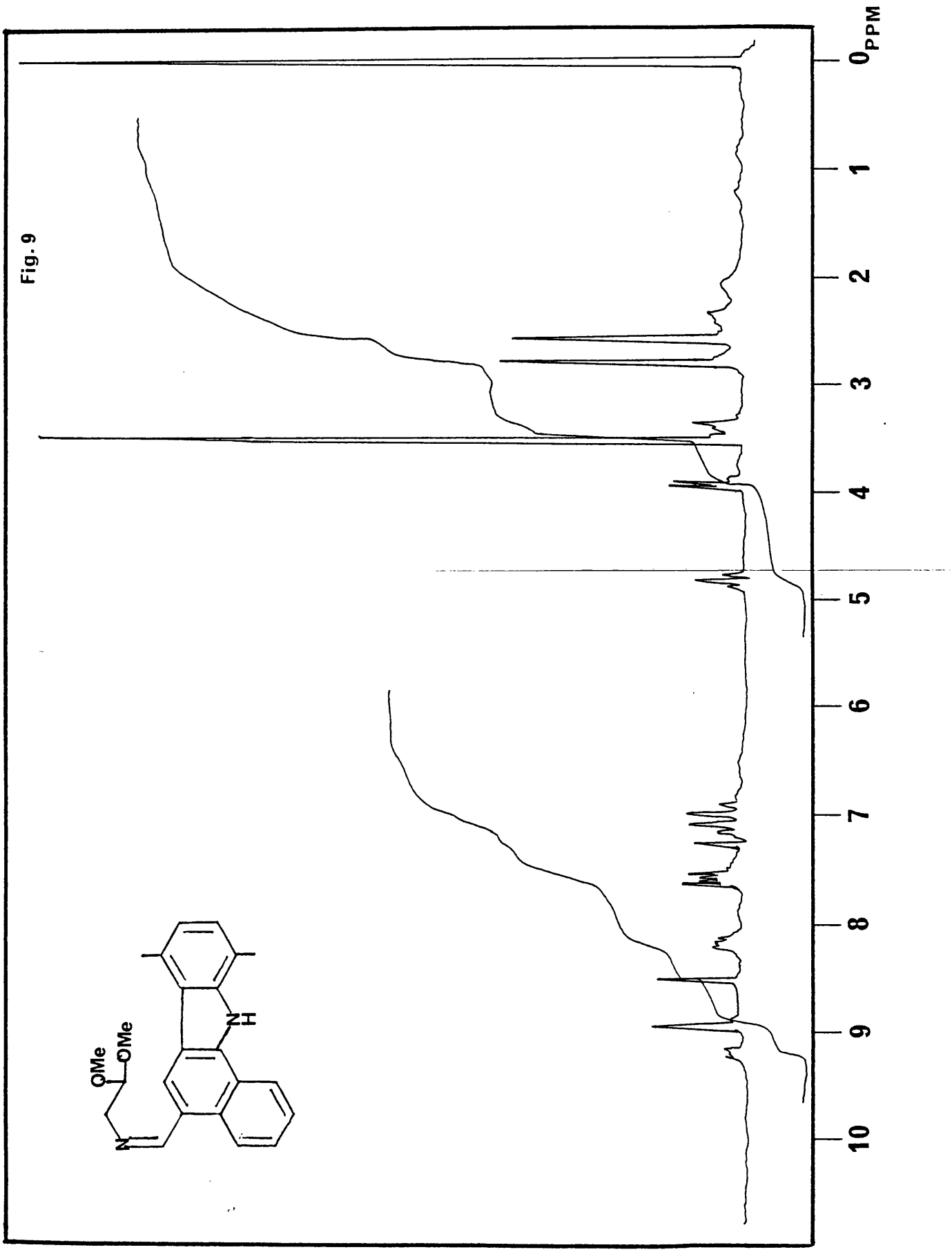


Fig. 9

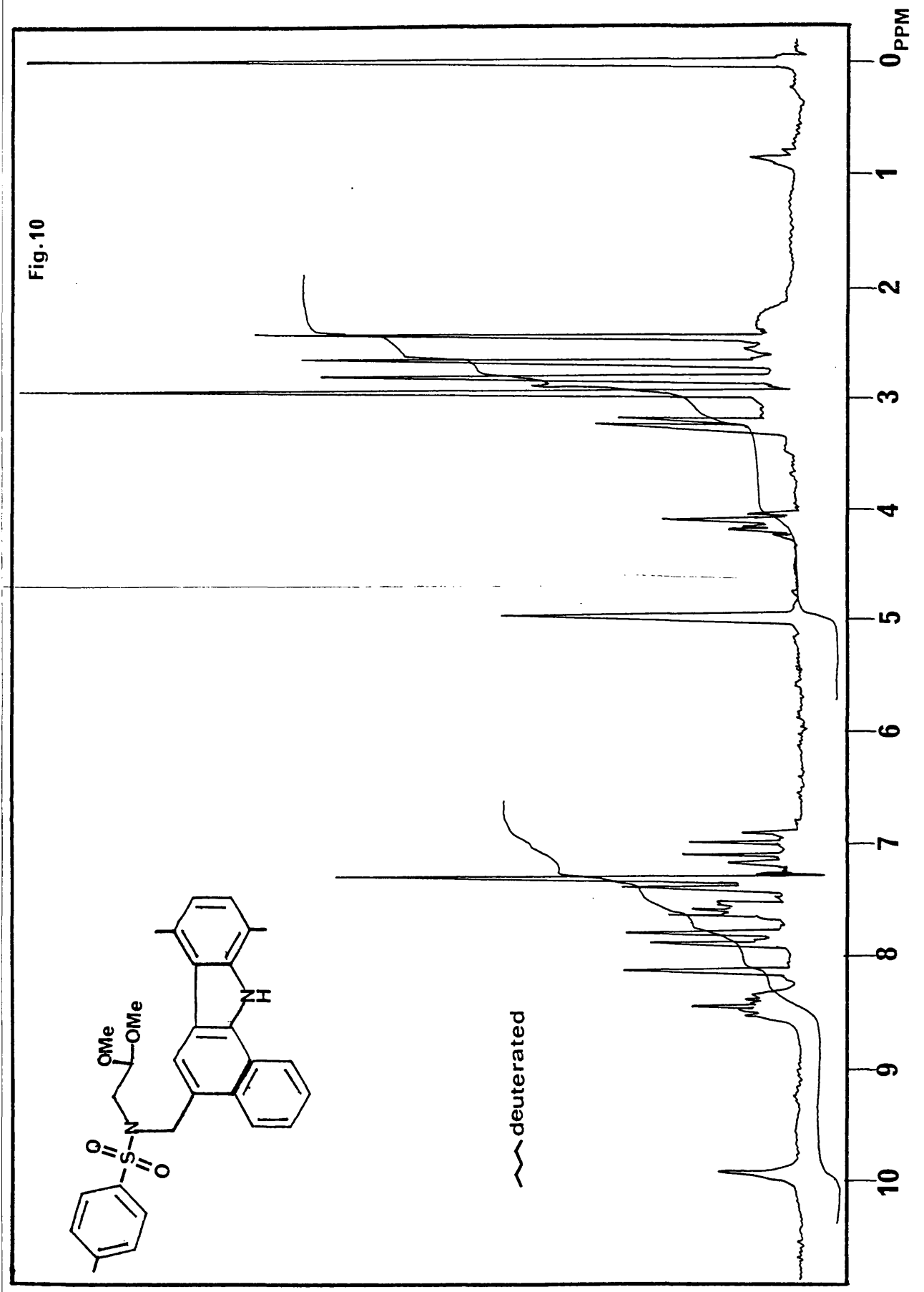
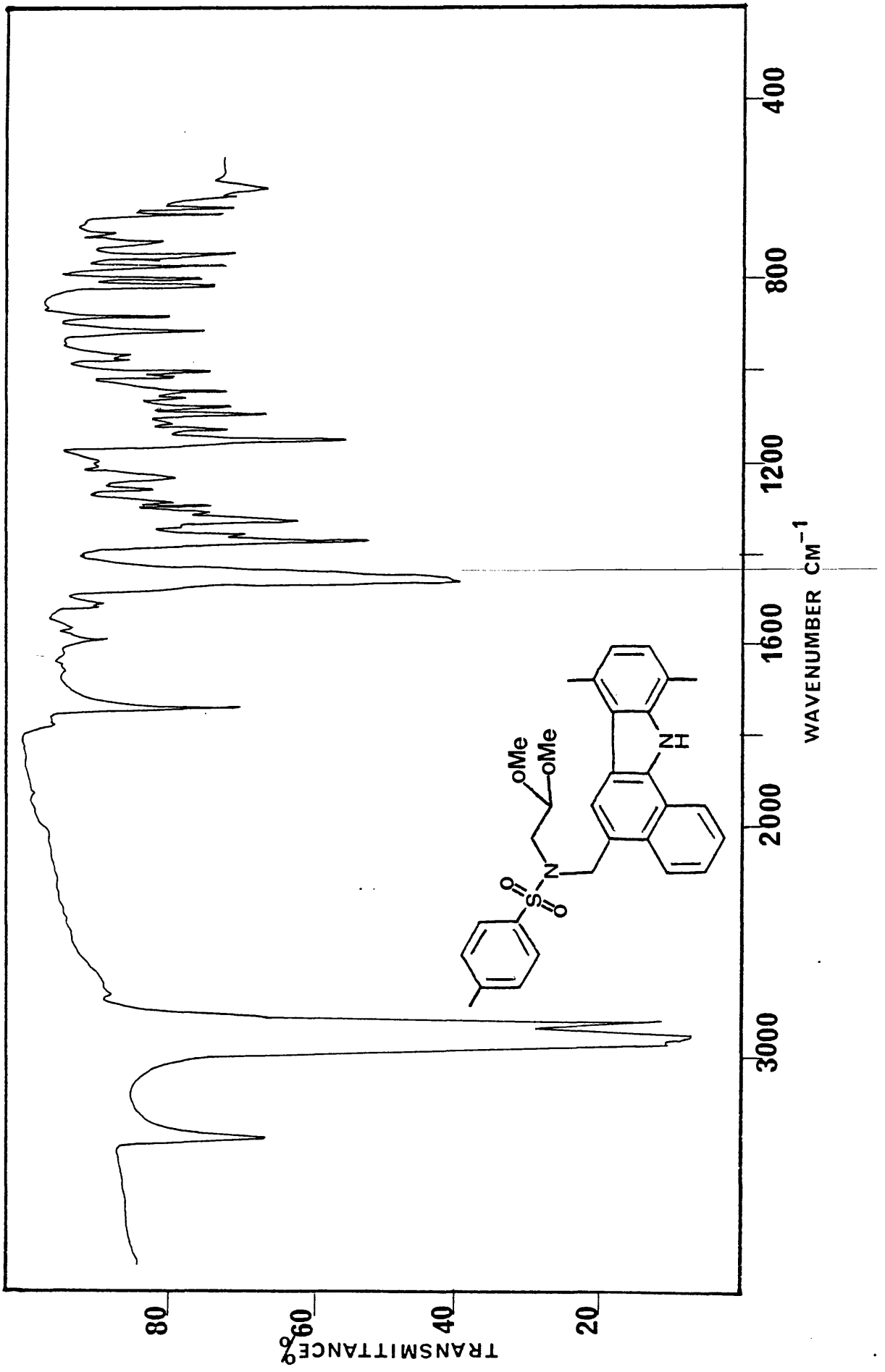


Fig.10


TRANSMITTANCE%
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60
40
20
3000
2000
1600
1200
800
400
WAVENUMBER CM^{-1}
oMe
oMe
S
O
O
N
H

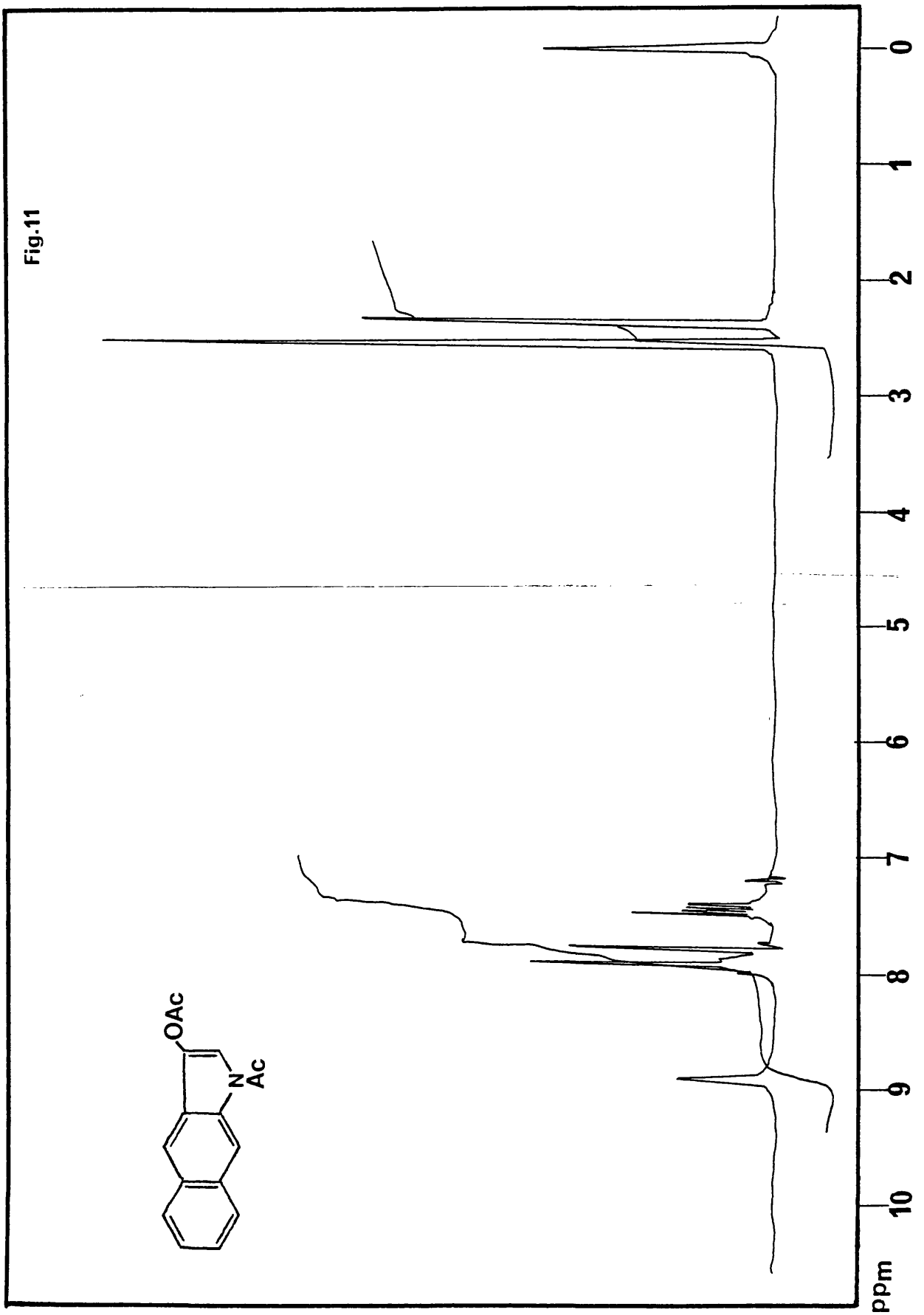
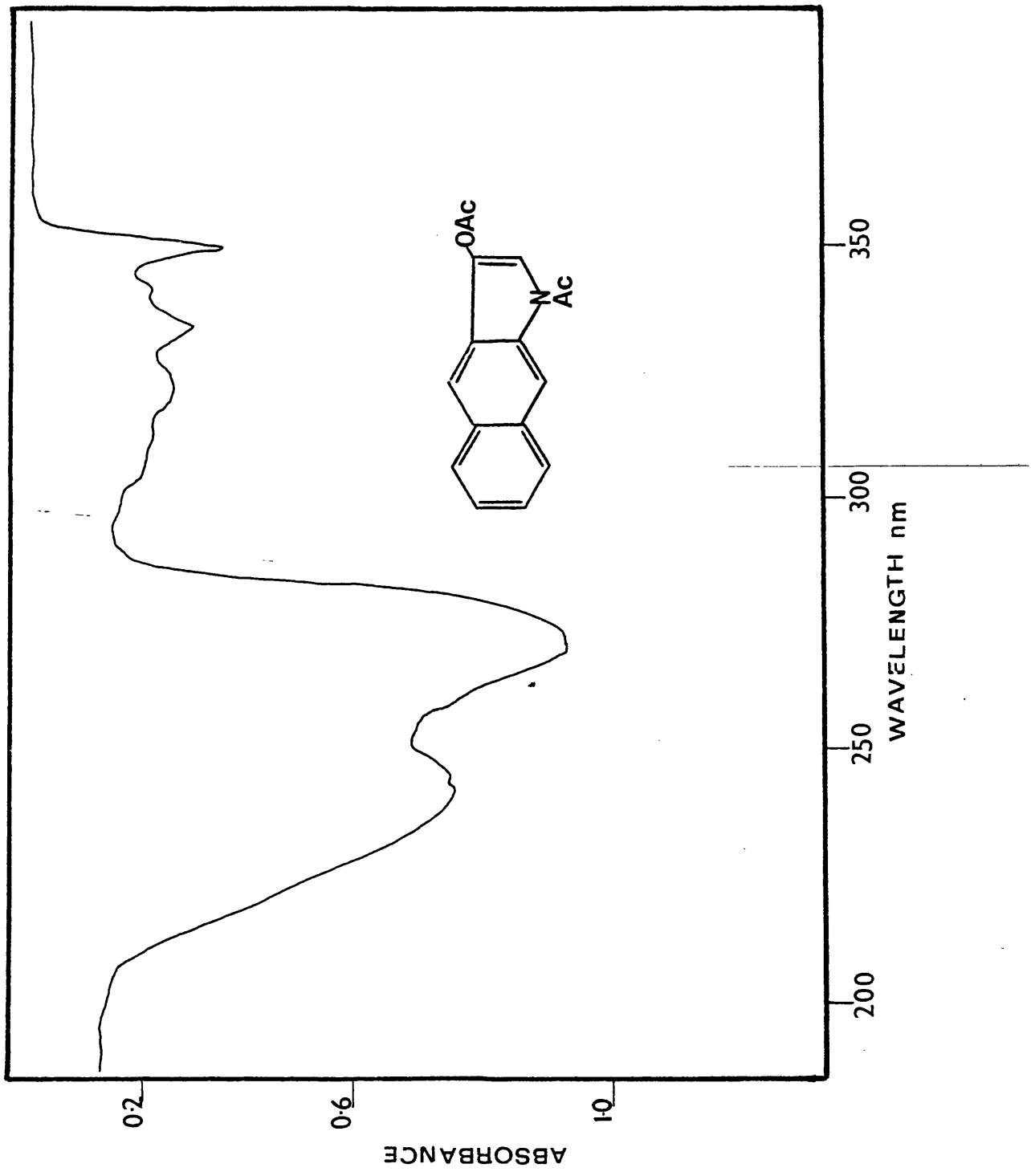
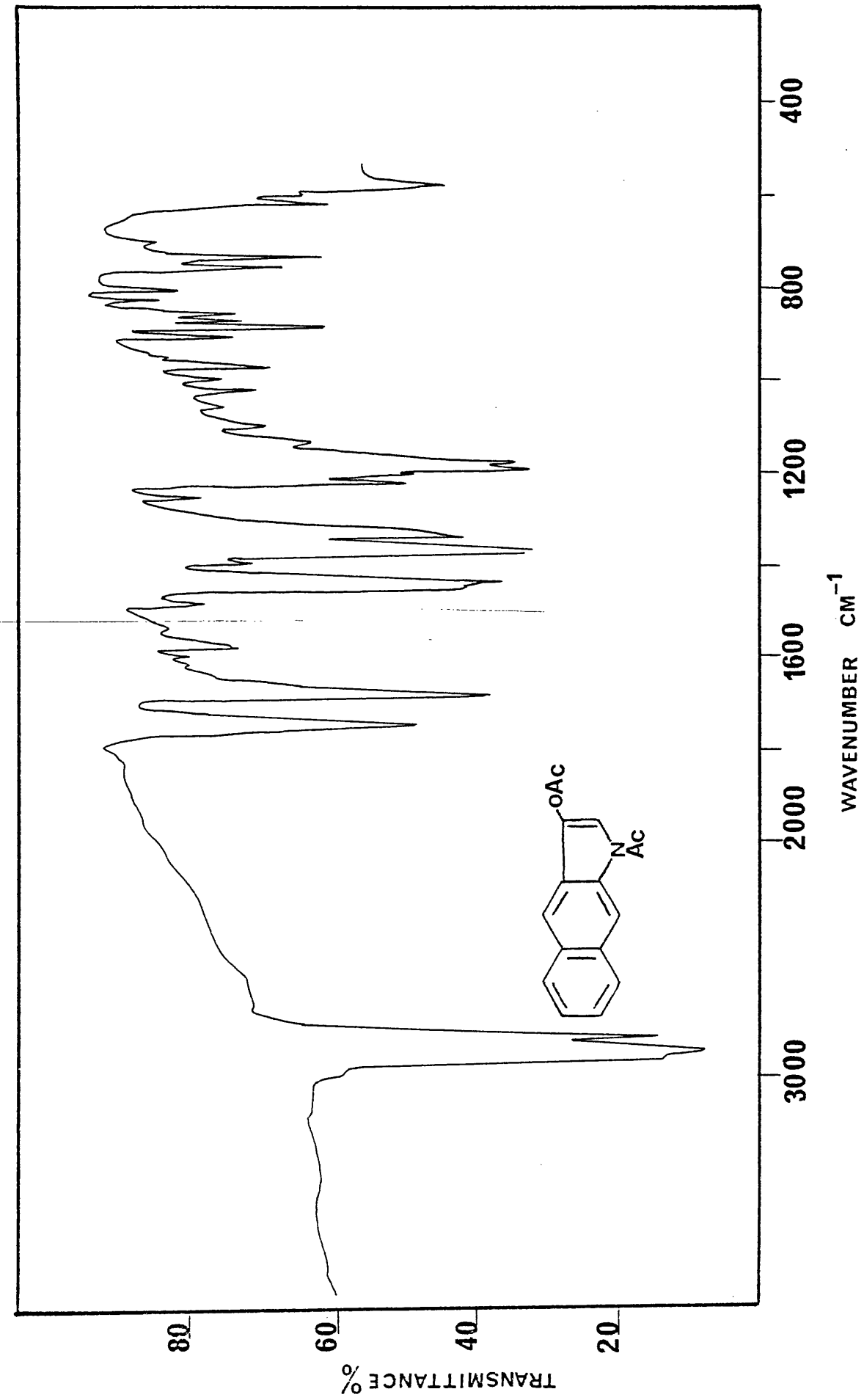


Fig.11


OAc
N
Ac
0·2
0·6
1·0
ABSORBANCE
200
250
300
350
WAVELENGTH nm


TRANSMITTANCE %
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400
WAVENUMBER CM^{-1}
OAc
N
Ac

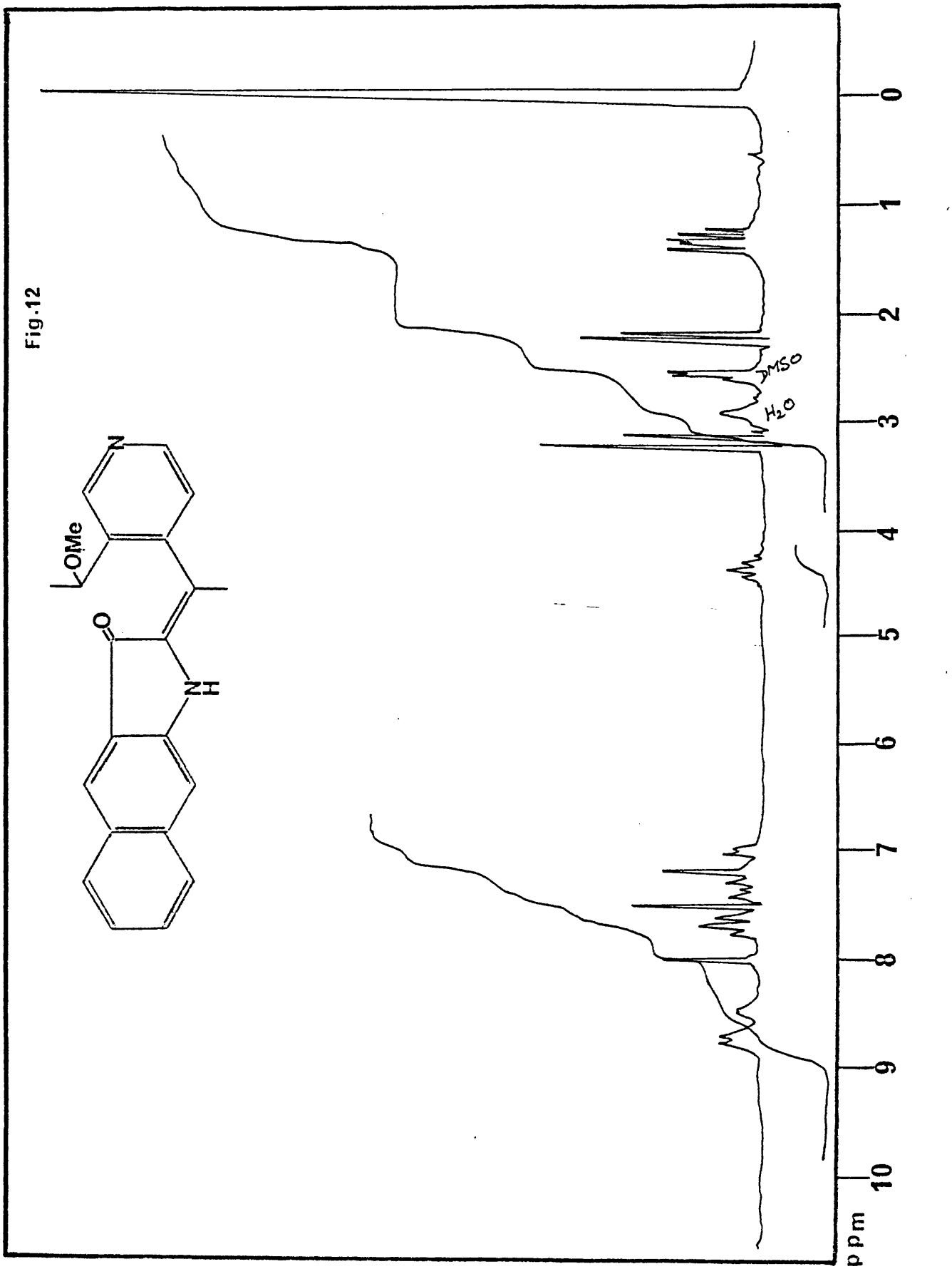
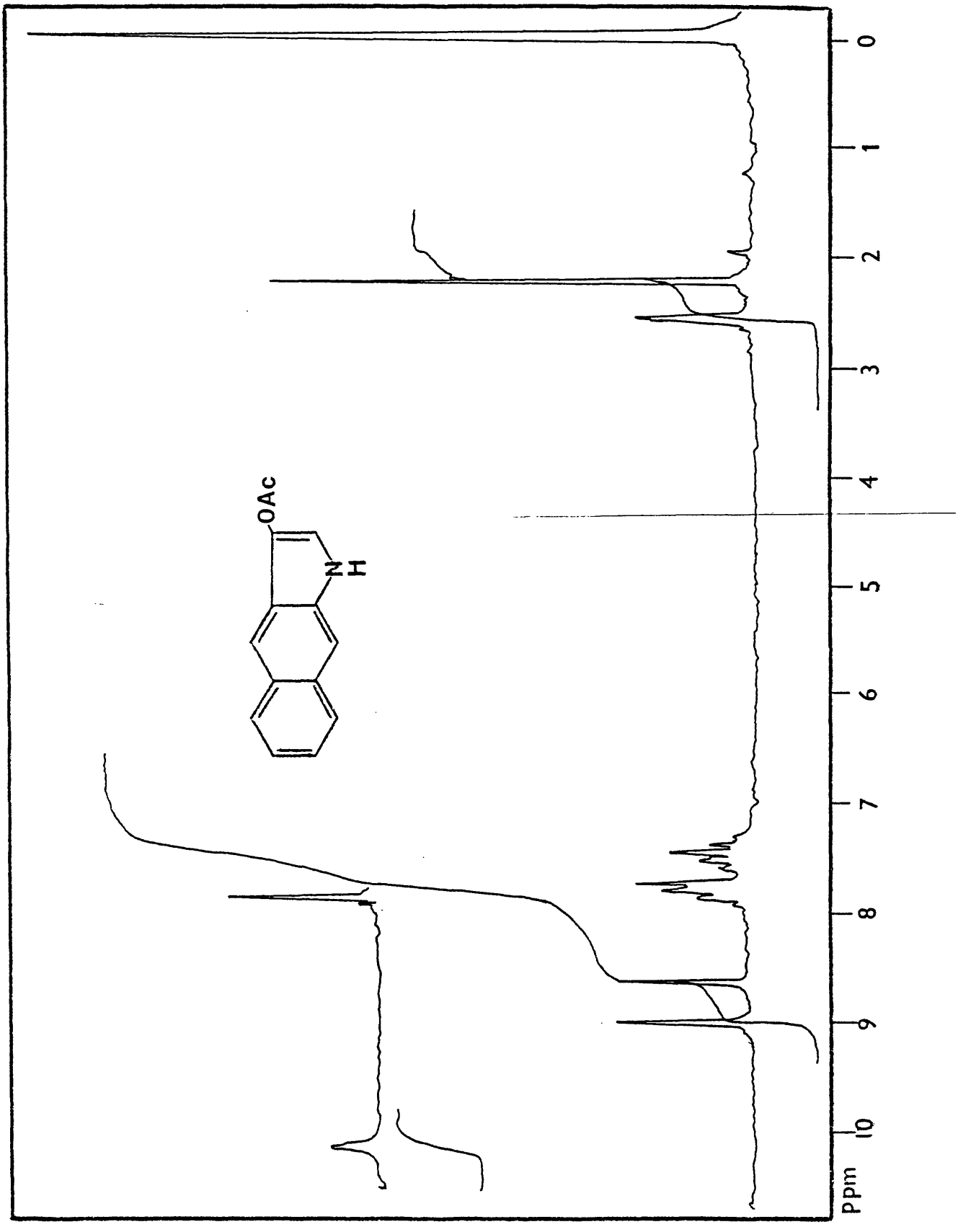


Fig.12


OAc
N
H
0
1
2
3
4
5
6
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10
Ppm

B I B L I O G R A P H Y

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